Uterine Myoma, Myomectomy and Minimally Invasive Treatments

Andrea Tinelli
Antonio Malvasi
Editors

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Editors
Andrea Tinelli
Gynecology and Obstetric
Vito Fazzi Hospital
Lecce
Italy

Antonio Malvasi
Obstetric and Gynecology
Santa Maria Hospital
Bari
Italy

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To my daughter, Laura. Wonderful was the day you entered my life, cheerfully and sweetly shocked. She inspired me to always work hard and try my best to honour her.

Andrea Tinelli

I dedicate this book to my father and my mother, who are no more among us, but from the sky they continue to drive my arm and my mind as happened in the creation of this book.

Antonio Malvasi

Preface

Uterine fibroids or myomas are the most common pelvic uterine tumors in women of childbearing age. They are benign monoclonal tumors arising from the smooth muscle cells of the myometrium. They could have negative impact on the reproductive system and can be single, but are more often multiple, causing significant morbidity and impairment of the quality of life. They are the leading indication for hysterectomies in the USA; nevertheless, epidemiological data on fibroid prevalence and incidence are limited and reliable population-based research is lacking. They arise in reproductive age women; estrogens and progestogens proliferate tumor growth as the fibroids rarely appear before menarche and regress after menopause. The majority of women with uterine fibroids are asymptomatic; consequently they get less clinical attention, and fibroid tumors often remain undiagnosed. Large numbers of patients with symptomatic fibroids typically present with symptoms of heavy or prolonged menstrual bleeding or pelvic pain and/or pressure. Additionally, women with uterine fibroids may suffer more often from dyspareunia, abnormal uterine bleeding and non-cyclic pelvic pain. Therapeutic options to treat these symptoms include medical therapy, surgical interventions and uterine artery embolization.

Scientific research in this topic is constantly evolving and is benefitting of many studies from various areas, such as molecular biology, genetics, endocrinology, pharmacology and biochemistry. Moreover, research also makes use of new diagnostic and surgical techniques which allow early recognition of fibroids and their removal by minimally invasive procedures, with the three most popular methods in use (hysteroscopy, laparoscopy and robotic surgery). Myomectomy can be performed in a number of ways depending on the location and number of lesions and the experience and preference of the surgeon.

It may not be possible to remove all lesions, nor will the operation prevent new lesions from growing.Surgical complications include the possibility of significant blood loss leading to blood transfusion, the risk of adhesions or scar formation in the uterus or within its cavity, and the possible need, if pregnancy ensues, to deliver the fetus by cesarean section. Myomectomy is associated with a possible risk of uterine rupture in later pregnancy.

This atlas will provide a full current knowledge on myomas and their well-known related problems. Each chapter is composed of many illustrations, photographs and images, largely in color, in order to better assist the reader

during the lecture. Covering recent advances in our understanding of myoma behaviour and an overview of the current options for their minimally invasive removal with endoscopy and new devices, *Uterine Myoma*, *Myomectomy and Minimally Invasive Treatments* brings together all the existing knowledge on this very common pathology in women of any age.

I particularly applaud the two friends, editors of the atlas, for having put together an outstanding group of worldwide experts providing a comprehensive discussion of basic research and clinical aspects of the topic. This atlas will help clinicians in gynecology, obstetrics, endocrinology, reproductive surgery, radiology and more to quickly understand how to best manage women with myomas. It will also help doctors, fellows and students to quickly and easily understand the recent advances on fibroid scientific knowledge.

Let me finally remark that the quality of figures and drawings is second to no other book on similar topic, and it is a specific asset of this enjoyable atlas.

Perugia, Italy

Gian Carlo Di Renzo, MD, PhD,
FACOG, FRCOG

Contents

Contributors

Ibrahim Alkatout Department Obstetrics and Gynecology, University Clinics Schleswig-Holstein, Kiel, Germany

Radu Apostol, DO Department of Obstetrics and Gynecology, St Luke's and Roosevelt Hospitals, New York, NY, USA

Erika Balassiano, MD Center for Special Minimally Invasive and Robotic Surgery, Stanford University Medical Center, Stanford, CA, USA

Hans A.M. Brölmann Department of Obstetrics and Gynaecology, VU University Medical Centre, Amsterdam, The Netherlands

Anupama Deenadayal Department Obstetrics and Gynecology, University Clinics Schleswig-Holstein, Kiel, Germany

Geraldine E. Ekpo, MD Division of Reproductive Endocrinology and Infertility, University of California San Francisco, San Francisco, CA, USA

Marina Eliseeva, MD, PhD Peoples' Friendship University of Russia, Moscow, Russia

Russian-German Center of Reproduction and Clinical Embryology, "Generation NEXT", Moscow, Russia

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia

Tommaso Falcone, MD Department of Obstetrics and Gynecology, Cleveland Clinic, Cleveland, OH, USA

Antonio Rosario Gargiulo, MD Department of Obstetrics, Gynecology and Reproductive Biology, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA

Richard J. Gimpelson Department of Obstetrics and Gynecology, Minimally Invasive Gynecology, Mercy Hospital St Louis, St Louis, MO, USA

Linnea R. Goodman, MD Department of Obstetrics and Gynecology, Cleveland Clinic, Cleveland, OH, USA

Marilena Greco, PhD Laboratory of Clinical Pathology,
Vito Fazzi Hospital, Lecce, Italy

Sergio Haimovich, MD Hysteroscopy Unit, Del Mar University Hospital,
Barcelona, Spain

Wouter J.K. Hehenkamp Department of obstetrics and Gynaecology,
VU University Medical Centre, Amsterdam, The Netherlands

Judith A.F. Huirne Department of Obstetrics and Gynaecology,
VU University Medical Centre, Amsterdam, The Netherlands

David Jay Levine, MD Department of Obstetrics and Gynecology,
Minimally Invasive Gynecologic Surgery, Mercy Hospital St Louis,
St Louis, MO, USA

Adam Magos, BSc, MBBS, MD, FRCOG University Department of
Obstetrics and Gynaecology, Royal Free Hospital, London, UK

Mohamad Mahmoud, MD Department of Obstetrics and Gynecology,
St Luke's and Roosevelt Hospitals, New York, NY, USA

Antonio Malvasi, MD Obstetric and Gynecology,
Santa Maria Hospital, Bari, Italy

International Translational Medicine and Biomodelling Research Group,
Department of Applied Mathematics, Moscow Institute of Physics and
Technology (State University), Moscow Region, Russia

Liselotte Mettler Department Obstetrics and Gynecology,
University Clinics Schleswig-Holstein, Kiel, Germany

Ospan A. Mynbaev, MD, MSc, PhD, ScD Peoples' Friendship
University of Russia, Moscow, Russia

International Translational Medicine and Biomodelling Research Group,
Department of Applied Mathematics, Moscow Institute of Physics and
Technology (State University), Moscow Region, Russia

Camran Nezhat, MD Center for Special Minimally Invasive
and Robotic Surgery, Stanford University Medical Center,
Stanford, CA, USA

Farr Nezhat, MD, FACOG, FACS Department of Obstetrics, Gynecology
and Reproductive Science Icahn School of Medicine,
Mount Sinai, USA

Division and Fellowship in Minimally Invasive Gynecologic Surgery
and Robotics, Division of Gynecologic Oncology, Department of Obstetrics
and Gynecology, Mount Sinai St Luke's and Mount Sinai Roosevelt,
USA

Department of Obstetrics, Gynecology and Reproductive Medicine,
State University of New York at Stony Brook, School of Medicine,
NY, USA

Minimally Invasive Gynecologic Surgery, Department of Obstetrics
and Gynecology, Winthrop University Hospital, NY, USA

Ceana Nezhat, MD, Prof, FACOG, FACS Department of Gynecology and Obstetrics, Emory University, School of Medicine, Atlanta, GA, USA

Departments of Obstetrics, Gynecology and Surgery, Stanford University Medical Center, Stanford, CA, USA

Nezhat Medical Center for Special Minimally Invasive Surgery and Reproductive Medicine, Atlanta, GA, USA

William H. Parker, MD Department of Obstetrics and Gynecology, UCLA School of Medicine, Los Angeles, CA, USA

George A. Pistofidis, MBBS. FROG Director of Gynaecological Endoscopic Surgery, Levkos Stavros Clinic, Athens, Greece

Leonardo Resta, MD Department of Emergency and Organ Transplantation (DETO), Section of Pathological Anatomy, University of Bari, Italy

Michael Stark, MD New European Surgical Academy (NESA), Berlin, Germany

Andrea Tinelli, MD Gynecology and Obstetric, Vito Fazzi Hospital, Lecce, Italy

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia

Daniel A. Tsin, MD, FACOG Department of Gynecology, Mount Sinai Hospital of Queens, Long Island City, NY, USA

Lindsey N. Valentine, MD Department of Obstetrics and Gynecology, Cleveland Clinic, Cleveland, OH, USA

Rafael F. Valle, MD Department of Obstetrics and Gynecology, Northwestern University Medical School, Chicago, IL, USA

Daniele Vergara Laboratory of General Physiology, Department of Biological and Environmental Sciences and Technologies, University of Salento, Lecce, Italy

Laboratory of Clinical Proteomic “Giovanni Paolo II” Hospital, ASL-Lecce, Lecce, Italy

Pathophysiology of Uterine Myomas and Its Clinical Implications

1

Rafael F. Valle and Geraldine E. Ekpo

Introduction

Uterine leiomyomas or, as frequently called, fibroids or myomas, are the most common solid pelvic tumors of the genital tract in women. Because of their frequency and bothersome symptomatology, they represent an onerous condition for women that often need to be dealt with medically. The majority of symptomatic women may require surgical treatment, as most medical approaches available at present, have not been completely successful, particularly in the long term. The pathophysiology of these tumors needs to be carefully reviewed and understood by physicians caring for women afflicted with this condition, in order to provide the best therapeutic option. This chapter will summarize the important factors involved in the pathophysiology of these tumors.

R.F. Valle, MD (✉)
Department of Obstetrics and Gynecology, Northwestern University Medical School, Chicago, IL 60611, USA
e-mail: rafaelvalle1@aol.com; r-valle@northwestern.edu

G.E. Ekpo, MD
Division of Reproductive Endocrinology and Infertility, University of California San Francisco, San Francisco, CA 94115, USA

Prevalence and Histogenesis

Although it is difficult to accurately determine the prevalence of uterine myomas in women, it has been estimated that 50–70 % of reproductive age women may be afflicted with uterine myomas [1]. Racial differences in prevalence have been found using ultrasonic evaluations even before these women become symptomatic, with a greater prevalence in black women as compared to white [2]. However, of women with ultrasonographic findings of myomas, only 20–50 % may become symptomatic [3]. It has been established that myomas are unicellular with an identical glucose-6-phosphate dehydrogenase electrophoretic type in each of its cells. Therefore, myomas seem to be unicellular in origin [3].

Factors Influencing Growth of Leiomyomas

There are multiple factors that lead to the growth of myomas but the most important ones are estrogens, progesterone and growth factors.

Estrogens (E)

In experimental studies estrogens were found to elicit the growth of myomas in guinea pigs. In some clinical observations, myomas grow

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larger during pregnancy and regress during the menopause signaling the important role of estrogens in their growth [3, 4].

Progesterone (P)

Progesterone seems to inhibit the growth of myomas in animal models producing intense degenerative changes. However, new evidence suggests that progesterone itself produces and plays an important role in the myoma growth and development (Fig. 1.1). Maruo et al. showed that Bcl-2 (Beta cell lymphoma-2) proto-oncogene, a unique cellular gene in its ability to block apoptotic cell death, is a survival gene that is increased in cultured myoma tissue. Bcl-2 is abundantly expressed in myomas obtained in the secretory phase of the menstrual cycle compared to the proliferative phase where progesterone levels are increased. No such cycle differences were seen in normal myometrial smooth muscle cells. The progesterone receptor mRNA is over-expressed in uterine myomas compared to that in the adjacent normal myometrium. The greater abundance of Bcl-2 protein in leiomyoma cells cultured in-vitro may be responsible for the growth of myomas by preventing apoptotic cell death [5]. Rein et al. have emphasized the critical role of progesterone in the pathogenesis of myomas by modulating somatic mutations of normal myometrium and the interaction with sex steroids and local growth factors, highlighting its importance among other multiple factors responsible for these mutations. Stimulation of the progesterone receptors by estrogen, epidermal growth factors and insulin like growth factor-1 (IGF-1) seems to contribute to the growth of myomas, and the increased mitotic activity in the secretory phase suggests that myoma growth is affected by progesterone. Progesterone induces up-regulation of the Ki-67 cell nuclear proliferation antigen, which is increased in myoma tissue. Also, there is clinical evidence of this interaction, as patients treated with GnRH-analogues plus progesterone demonstrated no significant reduction in uterine volume as evaluated with ultrasound, compared with those patients not treated with progesterone (Table 1.1) [6].

Fig. 1.1 Progesterone itself produces and plays an important role in the myoma growth and development

Table 1.1 Role of progesterone in the pathogenesis of uterine myomas: new theory

Progesterone contributes to regulation of mitotic activity
Estrogens stimulate progesterone receptors
There is increased mitotic activity in the secretory phase
Progesterone appears to inhibit GnRH-analogues induced hypo-estrogenism and shrinkage of myomas
Progesterone down regulates estrogen receptors
Progesterone induces up-regulation of the Ki-67 cell proliferation index
Progesterone up-regulates Bcl-2 protein expression, an apoptosis inhibitor in myoma cells

Growth Factors

Of the many growth factors that play a role in the myoma growth through synergistic actions with estrogens and progesterone, there are three that need mentioning: epidermal growth factor (EGF), vascular endothelial growth factor (VEG-F) and insulin-like growth factor (IGFs I-II). Also the extracellular matrix (ECM), a reservoir of growth factors that could promote leiomyoma growth, is an important factor to consider. All are responsible in the growth and development of myomas. EGF increases DNA synthesis in myoma cells. IGFs increase cell proliferation in myomas by activation of the MAPK (mitogen activated protein kinase) pathway involved in the proliferation of myoma cells. It also up-regulates Bcl-2 proliferation expression in myoma cells. VEG-F promotes angiogenesis in myomas [6, 7]. Finally, the ECM composed of collagen, fibronectin and proteoglycans, all involved in remodeling and growth of myomas. There is 50 % more ECM component in myomas than in the corresponding host myometrium. All these factors play a significant role along sex steroids in the development of myomas (Table 1.2) [7].

Cytogenetics

Forty percent of women affected with uterine myomas have cytogenetic abnormalities mainly comprised of rearrangements in C-12q14-q15, C-6p21 and C-10q, deletions in C-7q [7q22] and C-3, structural aberrations in C-6, and translocations in C-12 [8, 9]. About 50 % of myomas show clonal abnormalities involving chromosomes 1,7,12, and translocation (12;14). Whole-genome sequencing of myomas also show frequent fragmentation and random rearrangements similar to the chromothripsis phenomenon seen in malignant tumors (Table 1.3) [10, 11].

Table 1.2 Growth factors in myoma development

Epidermal growth factors (EGFs)
Insulin-like growth factors (IGFs-I, II)
Transforming growth factor-B
Heparin binding growth factors (HBGFs)
PDGF (platelet-derived GF)
BFGF (basic fibroblast GF)
VEGF (vascular endothelial GF)
HBEGF (heparin-binding epidermal GF)
Extracellular matrix

Table 1.3 Most frequent Cytogenetic alterations in Myomas

C-12q14-q15, C-6p21 and C-10q rearrangements
C-7q (7q22) and C-3 deletions
C-6 structural aberrations
C-12 translocations (14)

High Mobility Group 1 Proteins

These proteins have been found mainly in malignant and embryonic cells; however myomatous cells may also express these proteins, particularly HMG1, HMG1-C and HMG1 (Y), encoded in specific chromosomes that may have a role in the myoma growth. Normal myometrium does not harbor these proteins [12, 13].

Uterine Inner and Outer Myometrium

While the uterine myometrium looks anatomically uniform, two distinct zones have been described by Brosens et al. [14], showing that the junctional or inner myometrial zone and the outer myometrial zone are two distinct zones with

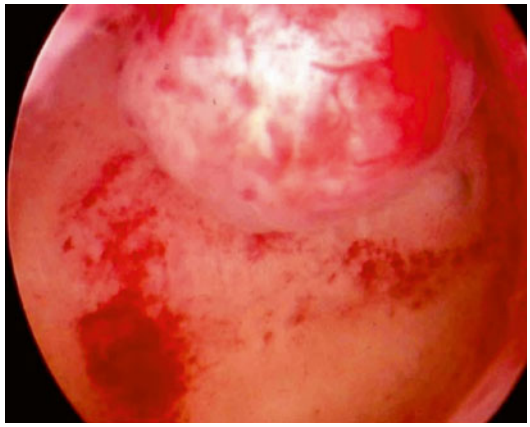

Fig. 1.2 Hysteroscopic view of fundal submucous myoma

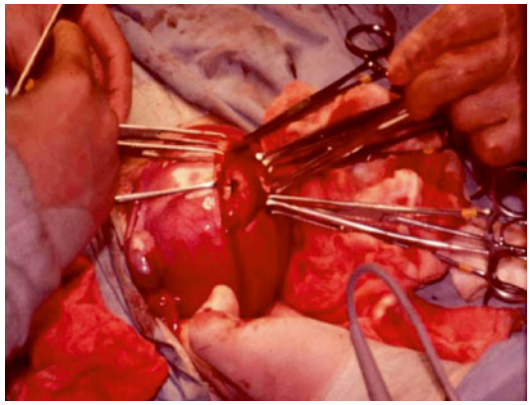

Fig. 1.3 Intramural myoma being removed by laparotomy

different pathophysiology. Myomas originating in each of these two zones respond differently to the ovarian hormones and their surrounding host myometrium is biochemically abnormal with increased cellular concentration of estrogen receptors, compared with normal myometrium. The junctional myometrium mimics the endometrium in its response to estrogen and progesterone and active contractions occur in the junctional myometrium throughout the menstrual cycle in contrast to the outer myometrium. Submucous myomas have less karyotypic aberrations than outer myometrial myomas and karyotypically abnormal myomas seem to be less hormone-dependent than myomas without chromosomal rearrangements. Also, GnRH-analogue therapy is more effective in size reduction of submucous myomas than outer myometrial layer myomas [15]. The arterial visualization in submucous myomas with Doppler ultrasonography is more markedly apparent (85 %) than in intramural myomas (42 %). These variations represent important factors to be considered in relation to reproduction and symptomatology (Figs. 1.2 and 1.3) [16].

Vascularization and Location of Uterine Myomas

Uterine myomas are parasitic tumors that borrow vascularization from the surrounding myometrium or other adjacent structures and when present, they may disrupt the delicate network that accompanies vascularization of the normal myometrium. This network originates from the uterine arteries extending to the arcuate and radial arteries and crossing the myometrium to reach the straight and spiral arteries that feed the endometrium. Disruption at any level of this vascular network will result in venous engorgement, dilatation and congestion that will disrupt the endometrium, producing abnormal bleeding and disrupting normal function and receptivity.

With the advancements in ultrasonography, hystero-sonography, 3-D ultrasonography and Doppler flow technology, the proper location and vascularization of myomas can be accurately determined and mapped to obtain information about location, number and size. Additionally, these modalities delineate the relationship of the myomas to the endometrium and uterine cavity, particularly in determining the percentage of uterine wall invasion of submucous myomas and their proximity to the uterine serosal surface (Figs. 1.4 and 1.5) [16].

These are important factors to consider in planning appropriate surgical treatment. Myomas have been classified according to their location in the uterine body: protruding away from the uterine body (subserosal), encased in the uterine muscle (intramural) and impinging at various degrees into the uterine cavity (submucosal). These locations determine the mode of surgical removal with or without invasion of the uterine muscular body (Figs. 1.6 and 1.7).

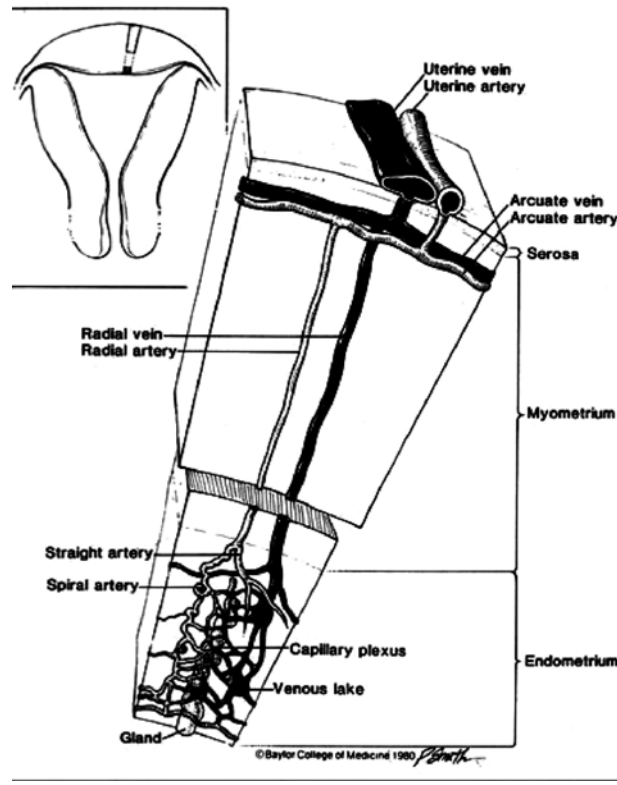

Fig. 1.4 Schematic representation of vascular network of a normal uterus. (Reprinted with permission from Elsevier, Inc.)

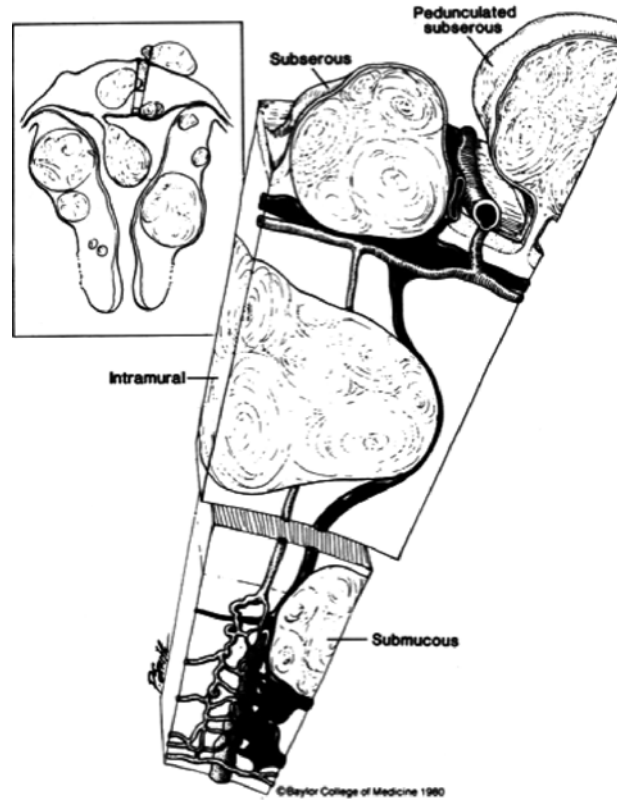

Fig. 1.5 Myomas obliterating and distorting the uterine vascularization at various sites of the uterine wall. (Reprinted with permission from Elsevier, Inc.)

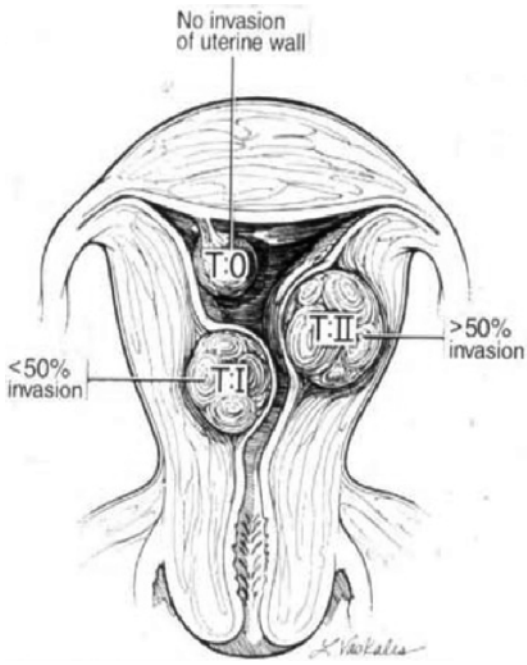

Fig. 1.6 Schematic representation of various invasions of the uterine wall by submucous myomas. (Reprinted with permission from Elsevier, Inc).

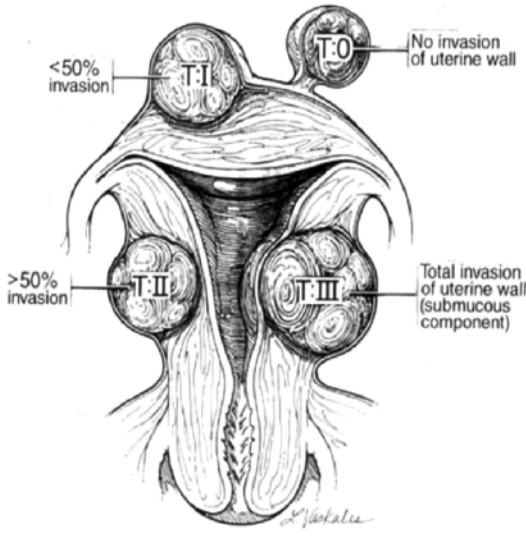

Fig. 1.7 Myomas impinging and penetrating the uterine wall from the periphery of the uterus. (Reprinted with permission from Elsevier, Inc).

Symptomatology of Uterine Myomas

The most frequent symptoms associated with myomas are: abnormal uterine bleeding, infertility, pregnancy losses and pelvic pain.

Abnormal Uterine Bleeding

Approximately 30 % of patients harboring uterine myomas present with abnormal uterine bleeding, especially submucous myomas where bleeding can be severe [3]. Many theories have been proposed to explain the pathophysiology of this symptom including coexisting associated anovulation, alteration of uterine contractility, compression of the venous plexi in the adjacent myometrium, increase in endometrial surface to more than 15 cm^2, erosion of the surface of submucous myomas and inability of the surrounding endometrium and myometrium to produce hemostasis [17]. However, none of these factors alone can satisfactorily explain the abnormal bleeding and perhaps all play a synergistic role (Figs. 1.8, 1.9, and 1.10) [3, 4].

Infertility

In an extensive and comprehensive review of the literature, Pritts [18] demonstrated that infertility could only be caused by submucous myomas and rarely by subserous or intramural myomas unless these latter types significantly distort or impinge the uterine cavity. In a retrospective analysis of 249 women with intramural myomas not distorting the uterine cavity who underwent in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI), Yan et al. found no adverse effects in the IVF/ICSI outcomes. However, when the intramural myomas were greater than 2.85 cm in size, there was a significant impairment in delivery rates in these patients compared with controls without myomas [19]. Subserosal and intramural myomas may only be coincidental to the infertility, as no objective evidence in their causal effect has been demonstrated in prospective randomized studies. Submucous myomas, however, may interfere with fertility and following treatment fertility is usually restored. There is evidence that submucous myomas not only produce local irritation and disruption of the intrauterine environment for implantation but also globally reduce intrauterine endometrial receptivity by interfering with specific molecular markers of endometrial receptivity such as HOXA 10 and HOXA 11

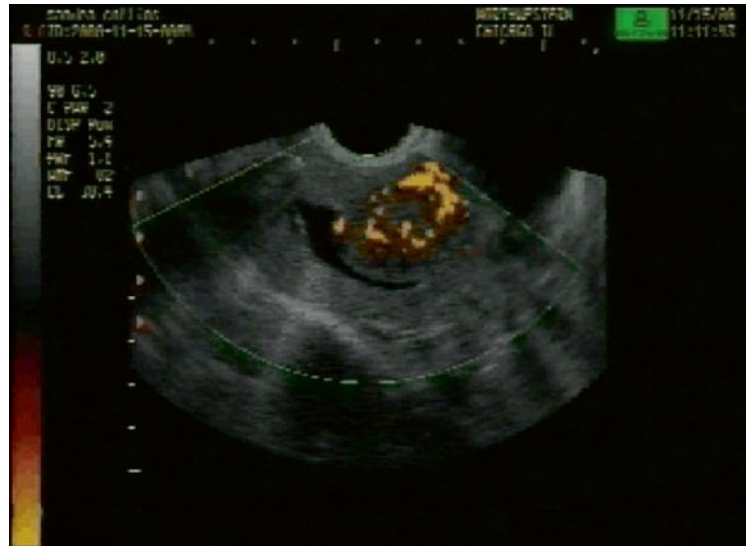

Fig. 1.8 Doppler flow aided ultrasonography demonstrating the peripheral vascularization of a submucous myoma

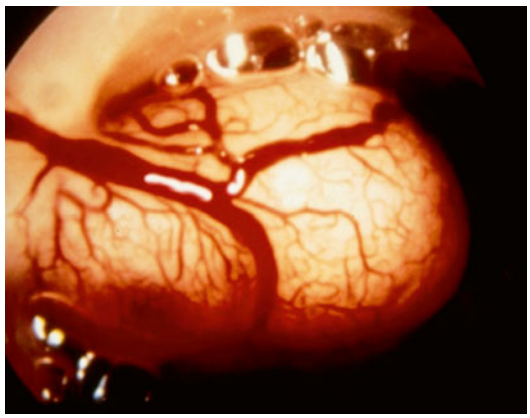

Fig. 1.9 Hysteroscopic view of submucous myoma showing its rich peripheral vascularization

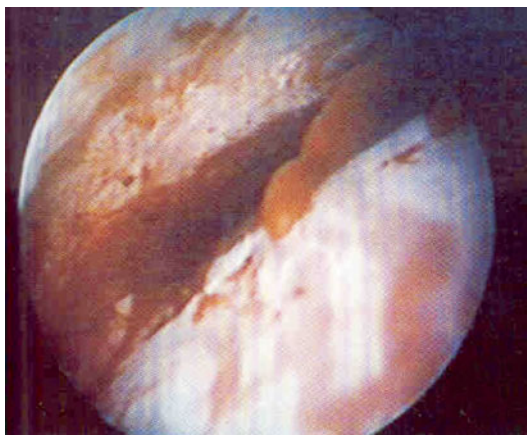

Fig. 1.10 Hysteroscopic view of active bleeding from a ruptured peripheral vessel of a submucous myoma

Table 1.4 Molecular markers of endometrial receptivity globally decreased by submucous myomas

HOXA 10
Leukemia inhibitor factor (LIF)
Basic transcriptional elemental binding protein 1 (BTEB 1)

gene expressions, LIF (leukemia inhibitor factor) and BTEB1 (basic transcriptional binding protein 1) [20]. Interestingly, when endometrial cells are cultured with fluid removed from hydrosalpinges, these molecular markers are suppressed and normalize when the hydrosalpinges are removed [21, 22]. So, this suggests that not only does the mere presence of the myomas in the uterine cavity impact endometrial receptivity, but also these tumors have a deleterious global effect on the molecular markers of endometrial receptivity (Table 1.4).

Spontaneous Abortions

Uterine myomas may interfere with the development of an established pregnancy resulting in early spontaneous abortion. Multiple factors may be responsible for this occurrence such as uterine irritability and contractility, oxytocinase or cystyl aminopeptidase deficiency and distortion of adequate blood supply interfering with fetal nutrition and normal development. About 40 %

Table 1.5 Uterine myomas: prevalence of preoperative symptoms

1,698 patients		
Pain N (%)	Menorrhagia N (%)	Infertility N (%)
58 (43)	504 (30)	454 (27)

Adapted from Buttram and Reiter [3]

of women afflicted with myomas may experience spontaneous abortions and this percentage is reduced by half following myomectomy [3, 4].

Pelvic Pain

Because pelvic pain may be due to multiple factors unrelated to myomas, such as adnexal adhesive disease, endometriosis, ovarian neoplasms, and adenomyosis, it is important to rule out such factors before attributing the pain to the presence of myomas. The pain may be directly related to the size and location of the myomas, therefore meticulous mapping of the myomas and their location by ultrasonography, and even magnetic resonance imaging when appropriate, is important to evaluate the tumors accurately. Pressure against other surrounding structures may cause pain as large myomas may compress the bladder, ureters and the recto-sigmoid bowel. Also, degeneration of myomas or torsion may occur and cause pain that is usually relived by surgical removal (Table 1.5) [3, 4, 23].

Promising New Medical Therapeutic Agents

Although GnRH-analogues have been useful for decreasing the volume and reducing abnormal bleeding from uterine myomas, their use is associated with bothersome symptomatology due to the marked hypo-estrogenism. Additionally, this mode of therapy cannot be used for pronged periods of time due to their untoward effects on bone density. Therefore when used for more than 6 months, add-back therapy with a progestational agent with or without estrogens is necessary to counteract this problem, following the threshold hypothesis that add-back therapy can relieve hypo-estrogenic symptoms, while maintaining their efficacy in treatment of the myomas. Also, there is a need to avoid the initial flare up of gonadotropins associated with the use of GnRH-analogues that worsens the symptomatology of myomas. For these reasons and based on the previously discussed pathophysiologic factors, new agents that could alleviate these problems and treat the myomas successfully are being tested. These include progesterone antagonists, selective progesterone receptor modulators and aromatase inhibitors [24, 25].

Progesterone Antagonists

Mifepristone or RU-486, a progesterone receptor antagonist, binds to progesterone, androgens and glucocorticoids receptors and was originally used for the medical termination of pregnancy. It inhibits progesterone receptor activation and reduces the number of progesterone-associated target effects. Used at the doses of 5–50 mg it was shown to reduce the size of myomas by up to 49 % after 3 months of treatment, decreasing the symptomatology of pelvic pressure, pain and abnormal bleeding. All the patients who received the drug developed amenorrhea. While no changes in bone mineral density were observed, mild hot flushes were reported and some transient mild increases in hepatic transaminases were observed but normalized within a month after the cessation of treatment [25, 26].

Selective Progesterone Receptor Modulators (SPRMs)

In an effort to avoid any of the side effects produced by Mifepristone and to further increase the effectiveness, new selective progesterone receptor modulators have been developed. These are: Asoprisnil, Proellex and Ulipristal Acetate.

Asoprisnil

A SPRM with progesterone receptor agonistic/antagonistic properties, Phase II multicenter double-blinded randomized trials with Asoprisnil demonstrated reduced myoma size and decreased menorrhagia. Also, a decrease in uterine artery blood flow was demonstrated in a dose dependent manner [27, 28].

Table 1.6 Selective progesterone receptor modulators (SPRM) and myomas

Inhibit blood flow at endometrial level
Suppress endometrial growth without decreasing estradiol levels
Decrease concentration of E and P receptors
Do not induce hot flushes or induce untoward effects on the bone
Decrease uterine size and myoma volume
Inhibit mitotic activity in myomas
Oppose the up-regulation of Bcl-2, and apoptosis inhibitor in myomas

Table 1.7 Aromatase inhibitors and uterine myomas

Aromatase inhibitors have an anti-estrogenic effect
They decrease peripheral conversion of androstenedione into estrogen
They act mainly in the suppression of in-situ estrogens and only weakly in the ovary
They have a negative effect on bone and lipid metabolism
Some women may develop joint problems (arthralgias)
Aromatase inhibitors do not increase risk of thromboembolism

Proellex (CDB-4124)

Proellex has been shown to be effective in decreasing the size of myomas and in reducing the associated symptomatology. However, due to the elevation of transaminases liver enzymes, the FDA has issued some restrictions until future clinical trials test the safety of the drug and efficacy at different doses [25].

Ulipristal Acetate (CDB-2914)

Ulipristal has pure progesterone antagonist activity. It has undergone several randomized trials showing effectiveness in reducing myoma size and the accompanied symptomatology. After 3 months of treatment, a 17–24 % decrease in uterine volume was seen in the Ulipristal group compared to a 7 % increase in volume in the placebo group. Doses of 5–10 mg of Ulipristal induced amenorrhea in 80 % of treated patients and did not decrease the estradiol levels below 50 pg/dl, a threshold thought to be important for maintaining bone mineral density [29, 30]. Under the trade name of Esmya, Ulipristal has been already approved for clinical use in Europe.

These SPRMs are promising agents to treat myomas, decreasing their size and producing amenorrhea in over 50 % of patients treated, however Phase III trials are needed to confirm their efficacy and safety, particularly their long term effects in endometrial stimulation, liver toxicity and bone mineral density (Table 1.6).

Aromatase Inhibitors (AIs)

Aromatase is a microsomal enzyme that catalyzes the conversion of androgens to estrogen. A member of the cytochrome P450 superfamily forms a functional enzyme complex with NADPH-cytochrome P450 reductase that is responsible for transferring reduced equivalents from NADPH to aromatase. Leiomyoma tissues have high aromatase activity while normal myometrium have little or no activity. Leiomyoma cells are able to synthesize sufficient estrogen to promote self growth, using circulating androstenedione as a substrate. It is likely that the differential inhibition of estrogen synthesis in-situ (in myomas) vs. in the ovaries results in leiomyoma regression by AI without the adverse effects associated with total estrogen deprivation, such as hot flushes and loss of mineral bone density [31]. AIs have a rapid onset of estrogen deprivation when administered and they do not have an initial flare-up period like the GnRH-analogues, therefore they can be started at any time of the menstrual cycle. Because estrogen depletion in the hypothalamus increases FSH and LH secretion causing ovarian stimulation, ovarian suppression needs to be added to AIs in the form of GnRH-analogues, progestins or combination oral contraceptives to avoid ovulation and unwanted conceptions. There are two types of AIs: the competitive AIs (Anastrazole and Letrozole) and the inactivator compounds (Exemestane). Both classes have been associated with decline of estrogen in blood and tissue to below postmenopausal levels [32]. Nonetheless, potential effects of long-term use, impact on future reproduction and the optimal dose needs to be clarified and determined for their use in premenopausal women (Table 1.7).

Based on the pathophysiologic factors involved in the growth and development of uterine myomas, these new medical therapeutic agents have been developed and offer great promise in the treatment of symptomatic myomas, while avoiding the side affects of presently available therapeutic agents. Additionally, these newer agents may be use to prepare patients for surgical removal of the myomas without the troubling secondary symptomatology from severe hypo-estrogenism produced by standard agents.

Summary and Conclusions

The pathophysiology of uterine myomas can be cumbersome and complex; easy to understand and to define as the main components are the ovarian sex steroids (estrogen and progesterone), and the synergistic action of growth factors. Many other factors, such as genetics, high-mobility group1 proteins also play a role in the complex network of interactions affecting the growth and development of uterine myomas but need further delineation.

To conclude,

- Uterine myomas are monoclonal in origin
- Myomas are regulated by sex steroid hormones, estrogen and progesterone (Fig. 1.11)
- Other factors may contribute to their growth in synergism with sex steroid hormones (growth factors, cytogenetic aberrations, high mobility group1 proteins)
- Inner and outer myometrium are two distinct entities with different pathophysiology and the myomas originating in these zones also differ in their expression levels of E and P receptors and consequently the myoma's growth and development
- Symptomatology depends on myoma size, location and vascular network distortion
- New medical agents such as progesterone antagonists, selective progesterone receptor modulators, and aromatase inhibitors offer a great promise in the medical treatment of these tumors.

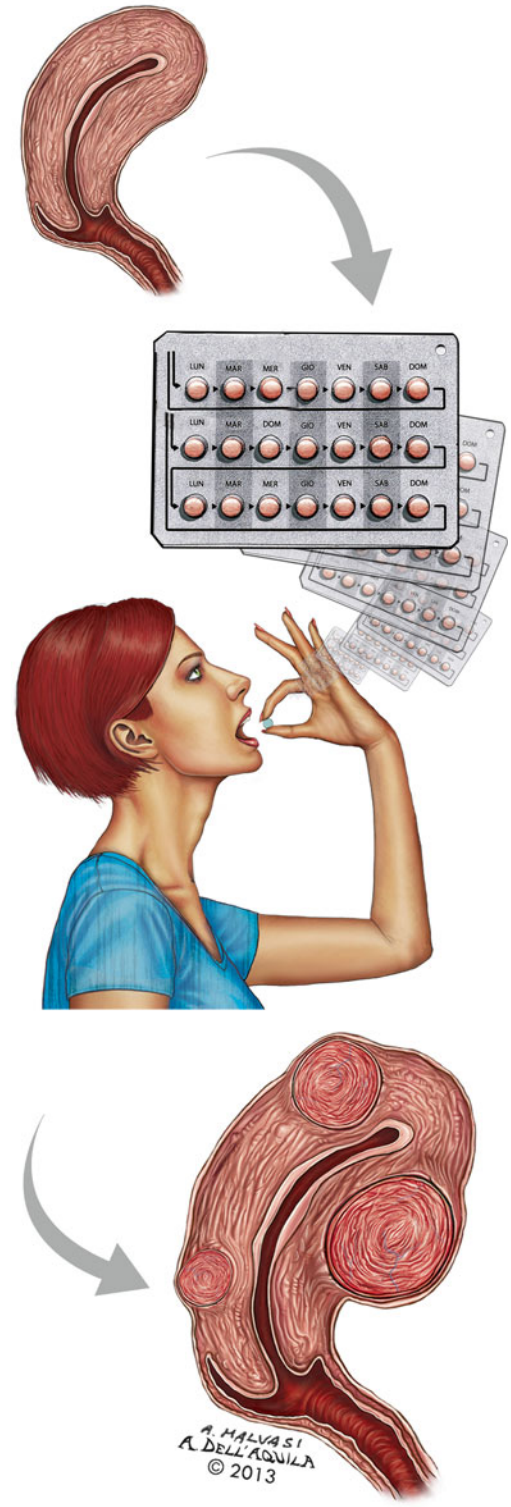

Fig. 1.11 Myomas are regulated by sex steroid hormones, estrogen and progesterone

References

1. Cramer SF, Patel A. The frequency of uterine myomas. Am J Clin Pathol. 1990;94:435–8.
2. Marsh EE, Ekpo GE, Cardozo ER, et al. Racial differences in fibroid prevalence and ultrasound findings in asymptomatic young women (18–30 years old): a pilot study. Fertil Steril. 2013;99:1951–7.
3. Buttram Jr VC, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril. 1981;36:433–45.
4. Wallach EE, Vlahas NF. Uterine myomas: an overview of development, clinical features, and management. Obstet Gynecol. 2004;104:393–406.
5. Maruo T, Matsuo H, Samoto T, et al. Effects of progesterone on uterine leiomyoma growth and apoptosis. Steroids. 2000;65:585–92.
6. Islam MS, Protic O, Stortoni P, et al. Complex networks of multiple factors in the pathogenesis of uterine leiomyoma. Fertil Steril. 2013;100:178–93.
7. Lewicka A, Osuch B, Cendrowski K, et al. Expression of vascular endothelial growth factor mRNA in human myomas. Gynecol Endocrinol. 2010;26:451–5.
8. Stewart EA, Morton CC. The genetics of uterine leiomyomata: what clinicians need to know. Obstet Gynecol. 2008;1007:917–21.
9. Brosens I, Johansson E, Dal Cin P, et al. Analysis of the karyotype and deoxyribonucleic acid content of uterine myomas in premenopausal, menopausal, and gonadotropin-releasing hormone agonist-treated females. Fertil Steril. 1996;66:376–9.
10. Meloni AM, Suoti U, Contento AM, et al. Uterine myomas: cytogenetic and histologic profile. Obstet Gynecol. 1992;80:209–17.
11. Brosens I, Duprest J, Cin PD, Van den Berghe H. Clinical significance of cytogenetic abnormalities in uterine myomas. Fertil Steril. 1997;69:232–5.
12. Megine M, Kaasinen E, Makinen N, et al. Characterization of uterine myomas by hole-genome sequencing. N Engl J Med. 2013;369:43–53.
13. Henning Y, Wanschura S, Deichert V, et al. Rearrangements of the high mobility group protein family genes and he molecular genetic origin of uterine myomas and endometrial polyps. Mol Hum Reprod. 1996;2:277–83.
14. Fuhrmann U, Wasserfall A, Klotzbucher M. Expression of high mobility group 1 proteins in uterine myomas. In: Brosens IA, Lunenfeld B, Donnez J, editors. Uterine fibroids. New York/London: Parthenon Publishing Group; 1999. p. 61–79.
15. Brosens J, Campo R, Gordts S, Brosens I. Submucosal and outer myometrium myomas are two distinct clinical entities. Fertil Steril. 2003;79:1452–4.
16. Cohen LS, Valle RF. Role of vaginal sonography and hysterosonography in the endoscopic treatment of uterine myomas. Fertil Steril. 2000;73(2):197–204.
17. Rogers R, Norian J, Malik M, et al. Mechanical homeostasis is altered in uterine leiomyoma. Am J Obstet Gynecol. 2008;198:474.e1–e11.
18. Pritts EA. Myomas and infertility; a systematic review of the evidence. Obstet Gynecol Surv. 2001;56:483–91.
19. Yan L, Ding L, Li C. Effect of myomas not distorting the endometrial cavity on the outcome of in vitro fertilization treatment: a retrospective cohort study. Fertil Steril. 2014;101:717–21.
20. Rackow BM, Taylor HS. Submucosal uterine myomas have a global effect on molecular determinants of endometrial receptivity. Fertil Steril. 2010;93(6): 2027–34.
21. Daftary GS, Taylor HS. Hydrosalpinx fluid diminishes endometrial cell HOXA 10 expression. Fertil Steril. 2002;78:577–80.
22. Daftary GS, Kayisli U, Seli E, Bukulmez ZO, Arici A, Taylor HS. Salpingectomy increases peri-implantation endometrial HOXA 10 expression in women with hydrosalpinx. Fertil Steril. 2007;87:367–72.
23. Klatzky PC, Tran ND, Caughey AB, Fujimoto VY. Myomas and reproductive outcomes: a systematic literature review from conception to delivery. Am J Obstet Gynecol. 2008;198:357–66.
24. Olive DL. Role of progesterone antagonists and new selective progesterone receptor modulators in reproductive health. Obstet Gynecol Surv (Suppl). 2002;57 Suppl 4:S55–63.
25. Stovall DW, Mikdachi HE. Treatment of symptomatic uterine myomas with selective progesterone receptor modulators. Expert Rev Obstet Gynecol. 2011;6: 579–82.
26. Murphy AA, Kettel LM, Morales AJ, et al. Regression of uterine leiomyomata in response to the antiprogesterone RU 486. J Clin Endocrinol Metab. 1993;76: 513–7.
27. Chwalisz K, Larsen L, Mattia-Golberg C, Edmonds A, Elger W, Winkel CA. A randomized, controlled trial of Asoprisnil, a novel selective progesterone receptor modulator, in women with uterine leiomyomata. Fertil Steril. 2001;87:1399–412.
28. Wilkens J, Chwalisz K, Han C, et al. Effects of the selective progesterone receptor modulator Asoprisnil on uterine artery blood flow, ovarian activity, and clinical symptoms in patients with uterine leiomyomata scheduled for hysterectomy. J Clin Endocrinol Metab. 2008;93:4664–71.
29. Levens ED, Potlog-Nahari C, Armstrong AY. CDB-2914 for uterine leiomyomata treatment: a randomized controlled trial. Obstet Gynecol. 2008;111: 1129–36.
30. Nieman LK, Blocker W, Nansel T, et al. Efficacy and tolerability of CDB 2914 treatment for symptomatic uterine myomas: a randomized, double blind, placebo controlled, Phase IIb study. Fertil Steril. 2011;95:767–72.
31. Shozu M, Murakami K, Inoue M. Aromatase and leiomyoma uterus. Semin Reprod Med. 2004;22: 51–60.
32. Folkerd EJ, Newton CJ, Davidson K, Anderson MC, James VH. Aromatase activity in uterine leiomyomata. J Steroid Biochem. 1984;20:1195–200.

Genetic and Genomics of Uterine Myomas

2

Daniele Vergara and Marilena Greco

Introduction

Uterine fibroids (also known as leiomyomas or myomas) are benign smooth muscle uterine tumors of unknown aetiology with a high incidence in women of reproductive age (Fig. 2.1). These kinds of lesions arise from myometrial transformation as a result of specific physiological and pathological conditions [1]. Uterine myomas are thought to be monoclonal tumors that occur via clonal expansion from a single mutated myometrial smooth muscle stem cell (Fig. 2.2) [2].

In the recent years, significant progress has been made in our understanding of myomas tumorigenesis. A current model suggests that a distinct stem/reservoir cell-enriched population, designated as the leiomyoma-derived side population (LMSP), is responsible to sustain proliferation and tumor growth [3].

Myomas are classified by their location relative to the layers of the uterus (as subserous, intramural, or submucous) and can occur as single or multiple tumors of varying size (Fig. 2.3) [4].

Leiomyomas are often asymptomatic but can cause a multitude of symptoms such as abnormal uterine bleeding, a feeling of pelvic pressure, urinary incontinence or retention, or pain [5].

The exact pathophysiology of uterine leiomyomas is still unknown, however several epidemiologic studies have linked uterine leiomyomas to different risk factors including high levels of female hormones (estrogens and progesterone), family history, African ancestry, early age of menarche and obesity. In contrast, it was found that childbearing at a later age is inversely associated with the risk of developing leyomyomas.

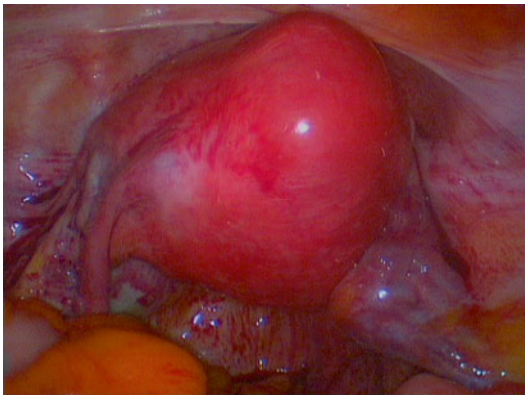

Fig. 2.1 A laparoscopic image of a uterus in reproductive age with a fundal myoma

D. Vergara (✉)
Laboratory of General Physiology,
Department of Biological and Environmental Sciences and Technologies, University of Salento,
Lecce, Italy

Laboratory of Clinical Proteomic,
"Giovanni Paolo II" Hospital,
ASL-Lecce, Lecce, Italy
e-mail: danielevergara@libero.it

M. Greco PhD
Laboratory of Clinical Pathology,
Vito Fazzi Hospital, Lecce, Italy
e-mail: marilena.greco@inwind.it

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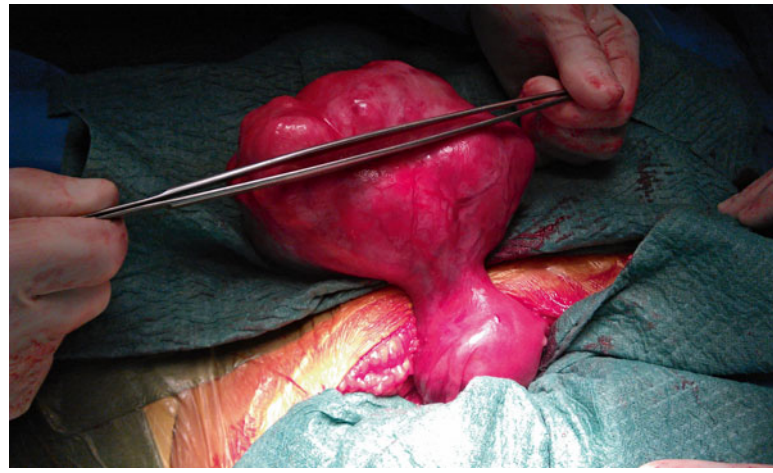

Fig. 2.2 A laparotomic image of a large fundal pedunculated myoma, as a benign smooth muscle uterine tumor that occur via clonal expansion from a single mutated myometrial smooth muscle stem cell

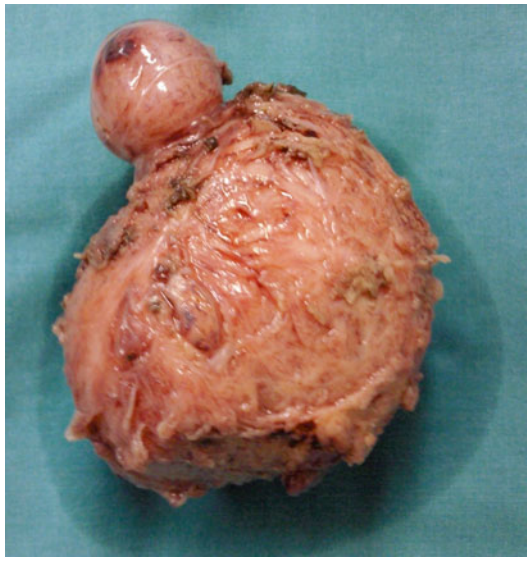

Fig. 2.3 An enucleated myoma composed by two tumors, one smallest and one larger

There has been recent evidence suggesting a relationship between alcohol and caffeine intake with a risk of developing fibroids. Metabolic, dietary, stress, and environmental factors may also play a role in fibroid development [5].

The traditional surgical options for myomas are hysterectomy and myomectomy, nonsurgical medical therapies are available but often ineffective in eliminating myomas and preventing recurrence.

Hormones have been considered as the major promoter of leiomyoma growth. In addition, several pathogenetic factors such as genetics, microRNA, growth factors, cytokines, chemokines have a role in the development and growth of the disease [6].

The mechanical properties of leiomyoma are another key feature of these tumors that may contribute to their growth. Leiomyomas are in fact stiff tumors characterized by an excessive deposition of disordered extracellular matrix (ECM) components, particularly collagen I, III, and IV, proteoglycans, and fibronectin [6]. Matrix metalloproteinases (MMPs) are implicated in leiomyoma remodelling with a higher activity of MMP-2 in leiomyomas than in surrounding myometrium [7]. Myomas are also surrounded by a thin fibro-neurovascular pseudocapsule, which separates myomas from normal peripheral myometrium [8]. This means that the tumor microenvironment may greatly influence tumor growth and proliferation.

Molecular Aspect of Uterine Leiomyomas

Uterine fibroid is a multifactorial and still enigmatic pathology. Classic studies showed steroid dependence of myomas for growth and development. The genetic background seems to play an important role, with cytogenetic anomalies observed in about 40 % of uterine fibroids. Abnormal ECM expression, increased growth

factors, cytokines and chemokines concentrations, and an extracellular disorganized matrix have been implicated in development and growth of uterine leiomyomas [9].

Most molecular studies of myomas have focused on the analysis of few genes or taken into account alterations in specific signalling pathways. These studies have revealed alterations of genes/proteins related to proliferation, cell-cycle regulation, apoptosis, and cell-cell adhesion.

Estrogens may exert their growth-stimulatory effects on leiomyomas through the action of a complex network of cytokines, growth factors, or apoptosis factors and through different cellular mechanisms [10]. In experiments with animal models, Ishikawa and collaborators suggested that estrogens induce the expression of the progesterone receptor (PR), thus supporting the action of progesterone on leiomyoma xenografts. Furthermore, estrogens may stimulate leiomyoma growth partially by suppressing normal p53 functions [11]. Biochemical and clinical studies also suggested that progesterone, progestins, and progesterone receptors (PR-A and PR-B) might increase proliferative activity in leiomyomas by enhancing the expression of growth factors (EGF, IGF-I) and apoptosis-related factors (TNFalpha, Bcl-2 proteins) [12].

Uterine myomas cells typically show a high expression of cell-cycle regulator and anti-apoptotic proteins. This can trigger tumor growth and make cells resistant to apoptosis.

Lora and collaborators demonstrated that the ratio between PR-A and PR-B is similar in normal myometrium and leiomyomas while p53 and p21 mRNA and protein levels are increased in leiomyomas [13]. Matsuo and collaborators showed that Bcl-2 protein, an apoptosis- inhibiting gene product, was abundantly expressed in myomas compared with normal myometrium. In this study, Bcl-2 protein expression in myoma cells was up-regulated by progesterone, but down-regulated by estradiol. The same group reported up-regulation of expression of proliferating cell nuclear antigen (PCNA) in myomas by progesterone and estradiol [14].

Wang and collaborators showed that protein and mRNA expression of bFGF and T-cadherin in uterine leiomyoma were present with significantly higher expression than that in adjacent normal myometrium and control normal myometrium. In addition, T-cadherin correlated well with bFGF. There was a relationship between T-cadherin and color Doppler flow imaging (CDFI) [15].

Epidemiological differences observed between different ethnic groups have a strong association with the genetic background. This is illustrated by a large-scale gene and protein expression-profiling study that provided valuable information about the molecular alterations of leiomyoma and myometrium in Caucasians and African Americans [16]. Data from genomic and proteomic studies demonstrated that many of the differences in leiomyoma's gene expression observed in the two ethnic groups might be attributed to differences in myometrial gene expression, as well as differences in leiomyomas vs. myometrium. Moreover, functional analysis of microarray and proteomic data revealed that many of the observed differences may be attributed to molecules with a role as transcriptional, translational and signal transduction mediators, cell cycle and EMC regulators, cell-cell adhesion and metabolic regulators. The current approach to diagnosis and treatment should evolve in the future and consider women with a greater genomic risk.

The Genomic Landscape of Uterine Myomas: Mutation Analysis and Chromosome Rearrangements

Several clinical evidences that allow the molecular characterization of this tumor support the presence of genetic mechanism involved in fibroids aetiology.

Somatic mutations involving the gene encoding the mediator complex subunit 12 (*MED12*) and the gene encoding the high-mobility group AT-hook 2 (*HMGA2*) are known to be associated to leiomyoma [1].

Mäkinen and collaborators [17] found that approximately 70 % of tumors contained heterozygous somatic mutations that affect *MED12*, a gene locates on the X chromosome. Authors

described that all mutations resided in exon 2 (codon 44), suggesting that aberrant function of this region of *MED12* contributes to tumorigenesis. Moreover, they also performed a pathway analysis, comparing eight tumors positive for *MED12* mutations with their respective normal tissues. Three pathways were found to be substantially altered in the tumors namely, focal adhesion, extracellular matrix receptor interaction, and Wnt signaling pathways. This suggests that *MED12* mutations contribute to tumor development by altering specific cellular pathways. The association between *MED12* and the Wnt pathway is also supported by the study of Markowski and collaborators which showed a significant upregulation of a member of Wnt pathway, *Wnt4*, in fibroids with *MED12* mutation compared to those with *HMGA2*. *Wnt4* is known to be expressed in the mesenchyme of the Müllerian duct giving rise to the likely tissue of origin of uterine leiomyomas. The overexpression of *Wnt4* in the group of fibroids with mutations of *MED12* compared to tumors with *HMGA2* rearrangement suggests that Wnt4 may be considered as a possibly relevant downstream effector of the mutated *MED12* [18].

MED12 belongs to a family of evolutionarily conserved transcriptional factors (Mediator) that promote the assembly, activation, and regeneration of transcription complexes on core promoters during the initiation and reinitiation phases of transcription (Fig. 2.4).

In detail, this gene codifies for a 26-subunit transcriptional regulator that bridges DNA regulatory sequences to the RNA polymerase II initiation complex. It is a subunit of the "kinase" module of the mediator complex, which also contains MED13, CYCLIN C, and Cyclin-dependent kinase 8 (CDK8). *MED12* is frequently mutated in human cancers including prostate [19], and renal cell carcinomas [20].

It was also observed that activation of ERK signaling by *MED12* suppression, may confer resistance to tirosin kinase inhibitors including crizotinib, gefitinib, vemurafenib, seluteminib, and sorafenib, thus providing a link between suppression of *MED12* and drug resistance. Data also indicate that *MED12* suppression induces an epithelial mesenchymal transition (EMT)-like phenotype and that this EMT-like phenotype induced by $MED12^{KD}$ is associated with chemotherapy resistance in both cell lines and patients [21].

Consistent with their role in the regulation of gene transcription, members of the Mediator family are functionally required for activated transcription in response to diverse cell signaling pathways. These include MED1 (TRAP220, ARC/DRIP205) for nuclear receptor, MED14 (TRAP170, ARC/DRIP/CRSP150 (cofactor required for Sp1 function) for interferon-γ, MED23 (TRAP150β, ARC/DRIP/CRSP130, human SUR2) for Ras/mitogen-activated protein kinase (MAPK), and MED15 (ARC105, PCQAP) for Transforming growth factor-β (TGF-β) signaling pathways [22, 23]. MED12 binds directly to β-catenin and regulates canonical WNT signaling [24]. Mechanism involving *MED12* mutations, WNT–β-catenin activation, and hyperactive TGF-β signaling supports stem-cell renewal, cell proliferation, and fibrosis in uterine fibroid tissue [25–27]. *MED12* has also been shown to modulate the sonic hedgehog (Shh) signaling pathway through Gli3 interaction [28]. As demonstrated by Mäkinen and collaborators, *MED12* mutations alone are sufficient for driving tumor development. Authors analysed whole exome sequencing data of 27 uterine leiomyomas (12 *MED12* mutation-negative and 15 *MED12* mutation-positive) and their paired normal myometrium. They searched for genes, which would be recurrently mutated. No such genes were identified in *MED12* mutation-negative uterine leiomyomas as well as *MED12* mutation-positive leiomyomas. These results highlight the unique role of MED12 mutations in genesis of uterine leiomyomas [29]. Moreover, it was recently demonstrated that pelvic and retroperitoneal leiomyomas harbor an increased frequency of *MED12* mutations (34 %) as compared with other extrauterine sites (0 %; $P = 0.0006$), and that histologically unremarkable adjacent myometrium can harbor similar *MED12* mutations suggesting that smooth muscle tumors in pelvic/retroperitoneal sites are subject to the same mutational changes as those of uterine myometrium [30].

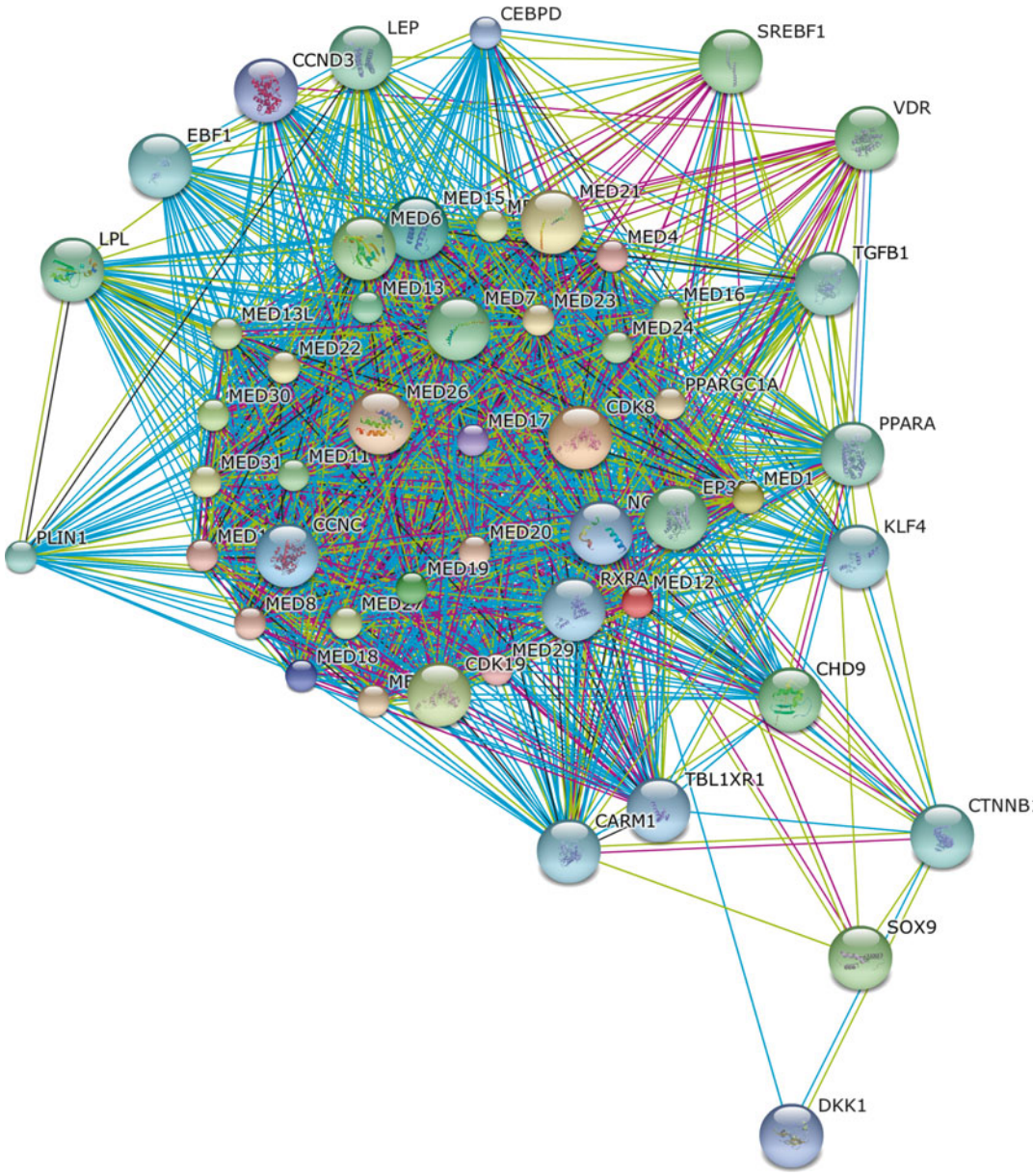

Fig. 2.4 The protein-protein interaction network of MED12 was determined using the online software STRING. The network nodes are proteins. The edges represent the predicted functional associations. An edge may be drawn with up to seven differently colored lines – these lines represent the existence of the seven types of evidence used in predicting the associations. A *red line* indicates the presence of fusion evidence; a *green line* – neighborhood evidence; a *blue line* – co-ocurrence evidence; a *purple line* – experimental evidence; a *yellow line* – textmining evidence; a *light blue line* – database evidence; a *black line* – co-expression evidence. Predicted functional partners include several members of the MED protein family, as well as transcriptional factors, microRNA, growth factors, and metabolic regulators

Although leiomyomas are belived to be chromosomally rather stable, cytogenetic rearrangements have been detected in 40–50 % of leiomyomas. Studies found translocation between chromosomes 12 and 14, trisomy 12, translocation between chromosomes 6 and 10 and deletion

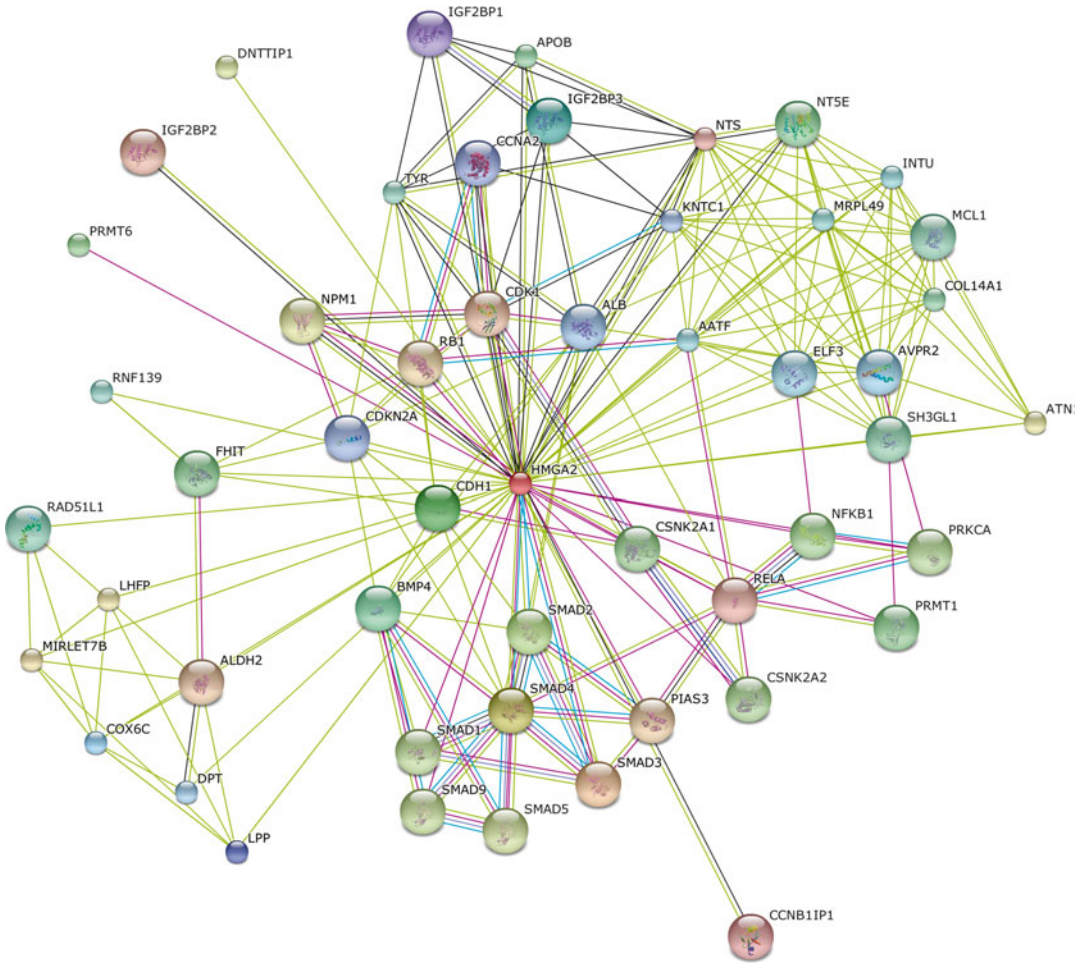

Fig. 2.5 The protein-protein interaction network of HMGA2 was determined using the online software STRING. The network nodes are proteins. The edges represent the predicted functional associations. An edge may be drawn with up to seven differently colored lines – these lines represent the existence of the seven types of evidence used in predicting the associations as described before. Predicted functional partners include several members of the SMAD protein family, PKC, microRNAs, cell cycle and metabolic regulators

of chromosomes 3 and 7, with multiple candidate genes [31–34]. Deletion of 7q, rearrangements involving 12q15 and 6p21 occur in 17, 20 and 5 % respectively [35, 36]. *HMGA2* is the driver gene for tumor carrying 12q15 rearrangements while high-mobility group AT-hook 1 (*HMGA1*) is involved in 6p21 rearrangements. The targeted translocation partner of *HMGA2* (and *HMGA1* in some cases) in leiomyoma is chromosomal band 14q24 [37–39]. The 14q24 breakpoint maps to a recombinational repair gene (*RAD51B*) locus [40], and the most frequent anomaly is t(12;14) (q14-15;q23-24).

HMGA2 is a protein that belongs to the non-histone chromosomal high mobility group (HMG) protein family which are often referred to as architectural proteins, participate in a wide variety of cellular processes including regulation of inducible gene transcription, integration of retroviruses into chromosomes, and the induction of neoplastic transformation and promotion of metastatic progression of cancer cells (Fig. 2.5).

They are characterized by the presence of 3 copies of a conserved DNA-binding peptide motif (AT-hook) that preferentially binds with the minor groove of many AT-rich promoter

and enhancer DNA regulatory elements. Protein-protein and protein-DNA interactions induce both structural changes in chromatin substrates and the formation of stereospecific complexes called 'enhanceosomes' on the promoter/enhancer regions of genes whose transcription they regulate [41, 42].

Aberrations in the chromosomal region 12q14-15 that affect *HMGA2* are frequent in a variety of tumours. In benign tumours of mesenchymal origin, *HMGA2* is often rearranged by translocation, and the resulting chimeric transcripts are formed by fusion of the DNA-binding domains, coded by exons 1–3, to ectopic sequences [43–45]; thus losing the C terminus and the 3′UTR region. In sarcomas, *HMGA2* is frequently and selectively amplified and rearranged [46].

The *HMGA2* 3′-UTR contains target sites for the let-7 miRNA, and thus the above mentioned rearrangements lead to over-expression of HMGA2 protein due to loss of miRNA-mediated repression [47, 48]. Furthermore, it appears that the balance between let-7 and HMGA2 governs the exit of cells from the undifferentiated and self-renewing state, and HMGA2 is now thought to be central in cancer in general [49–52]. *HMGA2* overexpression may favor self-renewal of mutated cells and offset senescence by suppressing cyclin-dependent kinase inhibitor 2a (*Cdkn2a*), which encodes the proteins p16Ink4a and p14Arf, negative regulators of their self-renewal [53]. Intriguingly, uterine fibroids are deficient in the let-7 miRNA that targets and suppresses *HMGA2* [54]. Kumar and collaborators [55] recently demonstrated that the oncogenic potential of the *HMGA2* gene is largely due to the ability of its transcript to operate as a competing endogenous RNA (ceRNA) in a protein coding-independent manner. The *HMGA2* mRNA decoys the let-7 microRNA family to regulate Tgfbr3 expression and enhance TGF-β signaling, thereby promoting lung cancer progression.

Most recently, the development of high informative genomic platforms provides further opportunities to characterise the molecular portrait of this tumor.

Mehine and collaborators performed a characterization of uterine leiomyoma by whole genome sequencing and gene expression profiling which showed that interconnected complex chromosomal rearrangements (CCRs) resembling chromothripsis (a single genomic event that results in focal losses and rearrangements in multiple genomic regions) were a common feature of leiomyoma and occurred in the presence of normal *TP53* alleles [56]. These rearrangements are best explained by a single event of multiple chromosomal breaks and random reassembly, which are a major cause of chromosomal abnormalities in uterine leiomyoma. The rearrangements appear responsible of tissue-specific changes consistent with a role in the initiation of leiomyoma. Rearrangements between chromosome 12 and 14, combining the 5′ end *RAD51B* with the full length high-mobility group AT-hook 2 (*HMGA2*), have been detected as a CCR event, and provide evidences that translocated *RAD51B* acts as an effective enhancer *HMGA2*. Further CCRs have been identified as translocation of *HMGA2* to chromosome 5, or as breakpoint in chromosome 12 that removes the *HMGA2* target sequence for the microRNA repressor let-7b, providing a mechanism of up-regulation of *HMGA2*. Other CCRs involving chromosomes 5 and 6 rearranged the full length *HMGA1* to the *MIR143HG*, encoding a precursor of the microRNAs miR-143 and miR-145, which regulate the differentiation of smooth-muscle cells [57]. Mehine and collaborators also identified aberration affecting collagen genes *COL4A5* and *COL4A6* on chromosome X22q. This locus is also constitutively disrupted in person with Alport's syndrome and diffuse leiomyomatosis [58] and it was associated of higher expression of insulin-receptor substrate 4 (*IRS4*) in leiomyoma [56]. In the same study CCRs resulting in deletion of 7q, which are common in uterine leiomyoma, have been associated to several rearrangements at various sites for target genes involved in response to DNA damage (*CUX1*) or CDK6-driven cell-cycle arrest at the G1 phase (*ZNHIT1*) or in the ubiquitine-dependent degradation of cell-cycle regulator (*CUL1*). Furthermore in the same study they found that *MED-12* mutated tumors had relatively few

chromosomal aberration while trancriptome analysis showed an up-regulation of *RAD51B* which further suggests a role of the gene in the pathogenesis of leiomyoma [56].

In different studies, other genes have been found to be implicated in leiomyoma development. Cha and colleagues [59] genotyped 1,607 individuals with uterine fibroids and identified 3 susceptibility loci associated with uterine fibroids. Chromosome 10q24.33 seems to have the best association with leiomyomas; the region was mapped to the 5′ region of the SLK gene encoding STE20-like kinase. STE20-like kinase has a role in myogenic differentiation, and, after activation by epithelial disruption, it is expressed in proliferating myoblasts. Another gene product located in the region is A-kinase anchor protein-13 (AKAP13), associated with cytoskeletal filaments. Related mutations could alter the regulation of extracellular matrix deposition and, consequently, of the fibrotic phenotype of the leiomyoma [60].

In addition to somatic mutations, heritable cancer syndromes can be characterized by uterine leiomyomas such as hereditary leiomyomatosis and renal cell cancer (HLRCC). This syndrome predisposes patients to benign leiomyomas of skin and uterus and early-onset renal cell carcinoma. The syndrome is caused by heterozygous germline mutations in the gene encoding fumarate hydratase (*FH*), an enzyme of the tricarboxylic acid cycle. Somatic *FH* mutations have been also reported in a small subset (1.3 %) of sporadic leiomyomas. Both hereditary and sporadic tumors are characterized by biallelic loss of *FH*, which would be predicted to cause severe metabolic stress [61, 62].

Epigenetics in Myomas

Epigenetic mechanisms are essential for normal development as well as for cancer initiation and progression. DNA methylation is one of the most commonly epigenetic events taking place in the mammalian genome and aberrant DNA methylation is a prominent characteristic of human cancer. This process affects gene activity by a covalent chemical modification, resulting in the addition of a methyl (CH3) group at the carbon 5 position of the cytosine ring. CpG dinucleotides are concentrated across the human genome in short CpG-rich DNA stretches called CpG islands.

DNA methylation is catalysed either by maintenance methyltransferases (DNMT1) or by de novo methyltransferases (DNMT3a and DNMT3b) that are active after completation of replication [63]. A global hypomethylation and differential expression of DNMT1, 3a and 3b, were revealed in uterine leiomyoma as compared with the matched normal myometria raising the possibility that epigenetic mechanisms such as DNA methylation and histone modification may contribute to the development of these tumors [64].

Several studies reported an aberrant promoter methylation of myomas-related genes such as *ER-α* (80 %), *DAP kinase* (54 %), *RASSF1A* (39 %), *p16INK4a* (22–25 %), and *MLH1* (6 %) [65–67] suggesting that global hypomethylation mechanisms may contribute to elevating the expression of these genes. Gloudemans and collaborators observed an inverse correlation between CpG methylation and expression of the insulin-like growth factor II (IGF-II) gene in malignant smooth muscle tissues. In normal smooth muscle and in leiomyomas the IGF-II gene appeared to be methylated, while in leiomyosarcomas with high IGF-II gene expression, the overall methylation of IGF-II gene tended to be low or absent [68].

Genomewide profiling of DNA methylation and messenger RNA (mRNA) expression in uterine fibroid tissue and matched normal myometrial tissue displayed hypermethylation at promoter sites that were associated with their silencing in the fibroid tissues [69]. In detail, authors identified a total of 585 transcriptional regulatory regions that were hypermethylated, and 446 were hypomethylated in uterine leiomyoma compared with adjacent normal myometrial tissue. They also considered the mRNA expression of these genes and observed that a total of 55 genes showed both differential DNA methylation and changes in mRNA

expression in uterine leiomyoma and adjacent normal myometrial tissue.

MicroRNAs (miRNAs) are a class of class of 18–24 nucleotide RNA molecules that regulate a high number of biological processes by targeting mRNAs for cleavage or translation repression. A direct link between miRNA expression and cancer pathogenesis is supported by several studies examining the expression of miRNAs in tumor samples [70].

The regulatory role of these small RNA molecules has recently begun to be explored in myomas, where several miRNAs such as let7, miR-21, miR-34a, miR125b, miR-93, miR-106b, and miR-200 are significantly dysregulated in uterine leiomyoma compared to those in normal myometrium [71, 72]. Global analysis of miRNA expression in leiomyomas from different racial groups showed that 31 miRNAs were expressed differently among different races. In particular, miR-21, miR-23a/b, miR-27a, miR-197, miR-203, miR-411, and miR-412 are significantly overexpressed in the leiomyomas of African-American women when compared with that in Caucasian women [71]. This suggests that a miRNA profile or, in general, a different molecular signature as described above, may account for the high morbidity rate of myomas in African-American women compared with women from other races.

Pathways Influencing Disease

Several signaling pathways are activated in uterine myomas. The role of the wingless-type (Wnt) pathway in supporting tumor initiation of myomas is well demonstrated [73]. The work of Ono and colleagues, demonstrated that the Wnt pathway could mediate molecular and cellular mechanisms involved in tumor initiation. Wnt acts as a paracrine signal from estrogen/progesterone receptor-rich mature cells to activate the canonical β-catenin pathway in leiomyoma stem cells to stimulate self- renewal and proliferation, eventually leading to tumor growth.

Other studies have demonstrated a central role for the phosphoinositide 3-kinase–protein kinase B/AKT (PI3K/AKT) pathway leading to the activation of mammalian target of rapamycin (mTOR) in the pathogenesis of leiomyomas [74]. A role for atypically activated mammalian target of rapamycin (mTOR) pathway in the pathogenesis of uterine fibroids has been reported in the study of Varghese and collaborators [75]. Authors demonstrated an aberrant expression of the G protein-coupled receptor 10 (GPR10), a G protein coupled-receptor with known functions in PI3K/AKT pathway activation, in uterine fibroids. They also observed that the transgenic overexpression of hGPR10 in mouse myometrium leads to leiomyoma phenotype. Moreover, they reported that RE1 suppressing transcription factor/neuron-restrictive silencing factor (REST/NRSF), a known tumor suppressor, transcriptionally represses GPR10 in the normal myometrium, and that the loss of REST in fibroids permits GPR10 expression. In conclusion they demonstrated that the loss of tumor suppressor REST and resulting activation of GPR10/PI3K/AKT/mTOR pathway play a role in the pathogenesis of uterine fibroids [75].

Perspectives

Our understanding of the human cancer genome landscape is expanding rapidly. Recent technological advances including next-generation sequencing approaches to nucleic acid sequencing provided an unprecedented opportunity for discovering genes and pathways associated with cancer in much greater detail. These approaches are now used to catalogue genomic aberrations driving the pathophysiology of main human tumors. The Cancer Genome Atlas (TGCA) represents the largest of such efforts (http://cancergenome.nih.gov/). Together with common genomic studies, these technologies were also applied to the study of uterine myomas leading to the conclusion that myomas have a distinctive biology at the cellular and molecular level. Molecular studies suggested that the genomic landscape of myomas is relatively simple (Table 2.1), dominated by driver mutations in two main genes *MED12* and *HMGA2* and other genetic aberrations, such as trisomy of

Table 2.1 Genetic abnormalities in uterine myomas

Event	Biological effect	Chromosome	Gene	References
Mutation	Activation of different signaling pathways	Xq13.1	*MED12*	[17]
	Metabolic stress	1q42.1	*FH*	[62]
Chromosomal changes (translocation, deletion, trisomy)	Cell growth, differentiation, apoptosis, and transformation	12q15	*HMGA2* [t(12;14)(q14-15;q23-24), most frequent]; *HMGA1*	[56]
		6p21 del(7)(q21-q32)	Rearragments at genes as *ZNHIT1*, *CUL1*, *CUX1*	
		12	/	
Differential Methylation	Several biological roles	/	585 transcriptional regulatory regions were hypermethylated, and 446 were hypomethylated in uterine leiomyoma compared with adjacent normal myometrial tissue	[69]
miRNA disregulation	Cell growth, survival	/	let7, miR-21, miR-34a, miR125b, miR-93, miR-106b, miR-200	[71, 72]

chromosome 12, deletions in 7q, and severe metabolic aberration (FH deficiency). These mutations occur at high frequency in patients with myomas. Overall, the results that emerge from these studies suggest that myomas have a unique mutation pattern respect to other human tumor types. For example, the TGCA genomic pattern is dominated by mutations in the *TP53* gene that is not mutated in myomas. Such differences are not surprising considering also the general benign nature of these tumors.

Moreover, given the importance of EMC in the control of tumor growth, future studies should focus on the cellular and molecular interactions between pseudocapsule and myoma. Targeting this tumor microenvironment may provide an important adjunct to current molecular therapeutics directed towards tumour cells.

Identification of new therapeutic targets is a central goal for controlling myomas. Currently, the management of myomas is based on the treatment by progestogens, a levonorgestrel-releasing intrauterine device, tranexamic acid, nonsteroidal anti-inflammatory drugs, or GnRH analogs [76]. The identification of deregulated signaling pathways such as Akt/mTOR and Wnt may provide opportunities for new therapeutic treatment.

Moreover, inhibitors already exist for high-mutated genes. Inhibitors of protein deacetylases represent a novel therapeutic option to influence HMGA2 expression. It was observed that Panobinostat strongly downregulated HMGA2 in HepG2 and Hep3B cells by transcriptional upregulation and promotion of the maturation of the tumor suppressor miRNA hsa-let-7b [77].

It also important to recognize that together with DNA mutations, alterations in other cellular components, including proteins or lipids, may be also important and the interplay between all these actors will probably provide new and relevant clinical insights. Pejić and collaborators observed that perturbation of antioxidant status is more pronounced in blood of patients with premalignant (hyperplastic) and malignant (adenocarcinoma) lesions, compared to those with benign uterine changes such as polypus and myoma [78]. Although information about the role of different signaling pathways highlight the role of proteins in the onset and development of myomas, comparative proteome profiling studies are still lacking. New proteomic approaches, such as MaldiImaging, make the analysis of proteins directly on tissues possible and affordable [79, 80].

References

1. Bulun SE. Uterine fibroids. N Engl J Med. 2013;369(14):1344–55.
2. Hashimoto K, Azuma C, Kamiura S, et al. Clonal determination of uterine leiomyomas by analyzing

differential inactivation of the X-chromosome-linked phosphoglycerokinase gene. Gynecol Obstet Invest. 1995;40(3):204–8.
3. Ono M, Qiang W, Serna VA, et al. Role of stem cells in human uterine leiomyoma growth. PLoS One. 2012;7(5):e36935.
4. Khan AT, Shehmar M, Gupta JK. Uterine fibroids: current perspectives. Int J Womens Health. 2014;6: 95–114.
5. Laughlin SK, Schroeder JC, Baird DD. New directions in the epidemiology of uterine fibroids. Semin Reprod Med. 2010;28(3):204–17.
6. Sozen I, Arici A. Interactions of cytokines, growth factors, and the extracellular matrix in the cellular biology of uterine leiomyomata. Fertil Steril. 2002; 78(1):1–12.
7. Bogusiewicz M, Stryjecka-Zimmer M, Postawski K, et al. Activity of matrix metalloproteinase-2 and -9 and contents of their tissue inhibitors in uterine leiomyoma and corresponding myometrium. Gynecol Endocrinol. 2007;23(9):541–6.
8. Malvasi A, Cavallotti C, Nicolardi G, et al. The opioid neuropeptides in uterine fibroid pseudocapsules: a putative association with cervical integrity in human reproduction. Gynecol Endocrinol. 2013;29(11): 982–8.
9. Ciavattini A, Di Giuseppe J, Stortoni P, Montik N, et al. Uterine fibroids: pathogenesis and interactions with endometrium and endomyometrial junction. Obstet Gynecol Int. 2013;2013:173184.
10. Olmos Grings A, Lora V, Dias Ferreira G, et al. Protein expression of estrogen receptors α and β and aromatase in myometrium and uterine leiomyoma. Gynecol Obstet Invest. 2012;73(2):113–7.
11. Ishikawa H, Ishi K, Ann Serna V, et al. Progesterone is essential for maintenance and growth of uterine leiomyoma. Endocrinology. 2010;151(6):2433–42.
12. Maruo T, Matsuo H, Shimomura Y, et al. Effects of progesterone on growth factor expression in human uterine leiomyoma. Steroids. 2003;68(10–13): 817–24.
13. Lora V, Grings AO, Capp E, et al. Gene and protein expression of progesterone receptor isoforms A and B, p53 and p21 in myometrium and uterine leiomyoma. Arch Gynecol Obstet. 2012;286(1):119–24.
14. Matsuo H, Kurachi O, Shimomura Y, et al. Molecular bases for the actions of ovarian sex steroids in the regulation of proliferation and apoptosis of human uterine leiomyoma. Oncology. 1999;57 Suppl 2:49–58.
15. Wang L, Mou X, Xiao L, et al. T-cadherin expression in uterine leiomyoma. Arch Gynecol Obstet. 2013;288(3):607–14.
16. Pan Q, Luo X, Chegini N. Genomic and proteomic profiling I: leiomyomas in African Americans and Caucasians. Reprod Biol Endocrinol. 2007;5:34.
17. Mäkinen N, Mehine M, Tolvanen J, et al. MED12, the mediator complex subunit 12 gene, is mutated at high frequency in uterine leiomyomas. Science. 2011;334: 252–5.
18. Markowski DN, Bartnitzke S, Löning T, et al. MED12 mutations in uterine fibroids their relationship to cytogenetic subgroups. Int J Cancer. 2012;131(7): 1528–36.
19. Barbieri CE, Baca SC, Lawrence MS, et al. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. Nat Genet. 2012;44(6):685–9.
20. Arai E, Sakamoto H, Ichikawa H, et al. Multilayer-omics analysis of renal cell carcinoma, including the whole exome, methylome and transcriptome. Int J Cancer. 2014. doi:10.1002/ijc.28768.
21. Huang S, Hölzel M, Knijnenburg T, et al. MED12 controls the response to multiple cancer drugs through regulation of TGF-β receptor signaling. Cell. 2012; 151(5):937–50.
22. Belakavadi M, Fondell JD. Role of the mediator complex in nuclear hormone receptor signaling. Rev Physiol Biochem Pharmacol. 2006;156:23–43.
23. Kato Y, Habas R, Katsuyama Y, et al. A component of the ARC/Mediator complex required for TGF beta/Nodal signalling. Nature. 2002;418(6898): 641–6.
24. Kim S, Xu X, Hecht A, Boyer TG. Mediatoris a transducer of Wnt/beta-cateninsignaling. J Biol Chem. 2006;281:14066–75.
25. Guo X, Wang XF. A mediator lost in the war on cancer. Cell. 2012;151:927–9.
26. Lee BS, Nowak RA. Human leiomyoma smooth muscle cells show increased expression of transforming growth factor-beta 3 (TGF beta 3) and altered responses to the antiproliferative effects of TGF beta. J Clin Endocrinol Metab. 2001;86:913–20.
27. Catherino WH, Leppert PC, Stenmark MH, et al. Reduced dermatopontin expression is a molecular link between uterine leiomyomas and keloids. Genes Chromosomes Cancer. 2004;40:204–17.
28. Zhou H, Kim S, Ishii S, et al. Mediator modulates Gli3-dependent Sonic hedgehog signaling. Mol Cell Biol. 2006;26(23):8667–82.
29. Mäkinen N, Vahteristo P, Bützow R, et al. Exomic landscape of MED12 mutation-negative and -positive uterine leiomyomas. Int J Cancer. 2014;134(4): 1008–12.
30. Schwetye KE, Pfeifer JD, Duncavage EJ. MED12 exon 2 mutations in uterine and extrauterine smooth muscle tumors. Hum Pathol. 2014;45(1):65–70.
31. Gross KL, Morton CC. Genetics and the development of fibroids. Clin Obstet Ginecol. 2001;4:335–49.
32. Ligon AH, Scott IC, Takahara K, et al. PCOLCE deletion and expression analyses in uterine leiomyomata. Cancer Genet Cytogenet. 2002;137:133–7.
33. Schoenmakers EF, Wanschura S, Mols R, et al. Recurrent rearrangements in the high mobility group protein gene HMGI-C, in benign mesenchymal tumourst. Nat Genet. 1995;10(4):436–44.
34. Quintana DG. ORC5L, a new member of the human origin recognition complex, is deleted in uterine leiomyomas and malignant myeloid diseases. J Biol Chem. 1998;273:27137–45.

35. Sandberg AA. Updates on the cytogenetics and molecular genetics of bone and soft tissue tumors: leiomyoma. Cancer Genet Cytogenet. 2005;158: 1–26.
36. Ligon AH, Morton CC. Genetics of uterine leiomyomata. Genes Chromosomes Cancer. 2000;28:235–45.
37. Fusco A, Fedele M. Roles of HMGA proteins in cancer. Nat Rev Cancer. 2007;7:899–910.
38. Kazmierczak B, Dal Cin P, Wanschura S, et al. HMGIY is the target of 6p21.3 rearrangements in various benign mesenchymal tumors. Genes Chromosomes Cancer. 1998;23:279–85.
39. Sornberger KS, Weremowicz S, Williams AJ, et al. Expression of HMGIY in three uterine leiomyomata with complex rearrangements of chromosome 6. Cancer Genet Cytogenet. 1999;114:9–16.
40. Ingraham SE, Lynch RA, Kathiresan S, et al. hREC2, a RAD51- like gene, is disrupted by t(12;14) (q15;q24.1) in a uterine leiomyoma. Cancer Genet Cytogenet. 1999;115:56–61.
41. Grosschedl R, Giese K, Pagel J. HMG domain proteins: architectural elements in the assembly of nucleoprotein structures. Trends Genet. 1994;10(3): 94–100.
42. Reeves R, Beckerbauer L. HMGI/Y proteins: flexible regulators of transcription and chromatin structure. Biochim Biophys Acta. 2001;1519(1–2):13–29.
43. Ashar HR, Fejzo MS, Tkachenko A, Zhou X, et al. Disruption of the architectural factor HMGI-C: DNA-binding AT hook motifs fused in lipomas to distinct transcriptional regulatory domains. Cell. 1995;82(1): 57–65.
44. Kazmierczak B, Wanschura S, Rosigkeit J, et al. Molecular characterization of 12q14-15 rearrangements in three pulmonary chondroid hamartomas. Cancer Res. 1995;55(12):2497–9.
45. Schoenmakers EF, Bunt J, Hermers L, et al. Identification of CUX1 as the recurrent chromosomal band 7q22 target gene in human uterine leiomyoma. Genes Chromosomes Cancer. 2013;52:11–23.
46. Berner JM, Meza-Zepeda L, Kools PF, et al. HMGIC, the gene for an architectural transcription factor is amplified and rearranged in a subset of human sarcomas. Oncogene. 1997;14(24):2935–41.
47. Mayr C, Hemann MT, Bartel DP. Disrupting the pairing between let-7 and Hmga2 enhances oncogenic transformation. Science. 2007;315(5818):1576–9.
48. Lee YS, Dutta A. The tumor suppressor microRNA let-7 represses the HMGA2 oncogene. Genes Dev. 2007;21(9):1025–30.
49. Langelotz C, Schmid P, Jakob C, et al. Expression of high-mobility-group-protein HMGI-C mRNA in the peripheral blood is an independent poor prognostic indicator for survival in metastatic breast cancer. Br J Cancer. 2003;88(9):1406–10.
50. Motoyama K, Inoue H, Nakamura Y, et al. Clinical significance of high mobility group A2 in human gastric cancer and its relationship to let-7 microRNA family. Clin Cancer Res. 2008;14(8): 2334–40.
51. Shell S, Park SM, Radjabi AR, et al. Let-7 expression defines two differentiation stages of cancer. Proc Natl Acad Sci USA. 2007;104(27):11400–5.
52. Yu F, Yao H, Zhu P, et al. Let-7 regulates self renewal and tumorigenicity of breast cancer cells. Cell. 2007; 131(6):1109–23.
53. Hammond SM, Sharpless NE. HMGA2, microRNAs, and stem cell aging. Cell. 2008;135:1013–6.
54. Peng Y, Laser J, Shi G, et al. Antiproliferative effects by Let-7 repression of high-mobility group A2 in uterine leiomyoma. Mol Cancer Res. 2008;6:663–73.
55. Kumar MS, Armenteros-Monterroso E, East P, et al. HMGA2 functions as a competing endogenous RNA to promote lung cancer progression. Nature. 2014;505: 212–7.
56. Mehine M, Kaasinen E, Mäkinen N, et al. Characterization of uterine leiomyomas by whole-genome sequencing. N Engl J Med. 2013;369(1): 43–53.
57. Cordes KR, Sheehy NT, White MP, et al. miR-145 and miR-143 regulate smooth muscle cell fate and plasticity. Nature. 2009;460:705–10.
58. Garcia-Torres R, Cruz D, Orozco L, et al. Alport syndrome and diffuse leiomyomatosis: clinical aspects, pathology, molecular biology and extracellular matrix studies: a synthesis. Nephrologie. 2000;21: 9–12.
59. Cha PC, Takahashi A, Hosono N, et al. A genome-wide association study identifies three loci associated with susceptibility to uterine fibroids. Nat Genet. 2011;43(5):447–50.
60. Rogers R, Norian J, Malik M, et al. Mechanical homeostasis is altered in uterine leiomyoma. Am J Obstet Gynecol. 2008;198(4):474.e1–11.
61. Lehtonen R, Kiuru M, Vanharanta S, et al. Biallelic inactivation of fumarate hydratase (FH) occurs in nonsyndromicuterine leiomyomas but is rare in other-tumors. Am J Pathol. 2004;164:17–22.
62. Lehtonen HJ. Hereditary leiomyomatosisand renal cell cancer: update onclinical and molecular characteristics. Fam Cancer. 2011;10:397–411.
63. Reik W. Stability and flexibility of epigenetic gene regulation in mammalian development. Nature. 2007;447(7143):425–32.
64. Li S, Chiang TC, Richard-Davis G, et al. DNA hypomethylation and imbalanced expressionof DNA methyltransferases (DNMT1, 3A, and 3B) in human uterine leiomyoma. Gynecol Oncol. 2003;90:123–30.
65. Asada H, Yamagata Y, Taketani T, et al. Potential link between estrogen receptor-alpha gene hypomethylation and uterine fibroid formation. Mol Hum Reprod. 2008;14(9):539–45.
66. Kawaguchi K, Oda Y, Saito T, et al. Mechanisms of inactivation of the p16INK4a gene in leiomyosarcoma of soft tissue: decreased p16 expression correlates with promoter methylation and poor prognosis. J Pathol. 2003;201(3):487–95.
67. Kawaguchi K, Oda Y, Saito T, et al. Death-associated protein kinase (DAP kinase) alteration in soft tissue leiomyosarcoma: promoter methylation or

homozygous deletion is associated with a loss of DAP kinase expression. Hum Pathol. 2004;35(10): 1266–71.
68. Gloudemans T, Pospiech I, Van Der Ven LT, et al. Expression and CpG methylation of the insulin-like growth factor II gene in human smooth muscle tumors. Cancer Res. 1992;52(23):6516–21.
69. Navarro A, Yin P, Monsivais D, et al. Genome-wide DNA methylation indicates silencing of tumor suppressor genes inuterine leiomyoma. PLoS One. 2012;7(3):e33284.
70. Hwang HW, Mendell JT. MicroRNAs in cell proliferation, cell death, and tumorigenesis. Br J Cancer. 2006;94(6):776–80.
71. Wang T, Zhang X, Obijuru L, et al. A micro-RNA signature associated with race, tumor size, and target gene activity in human uterine leiomyomas. Genes Chromosomes Cancer. 2007;46(4):336–47.
72. Marsh EE, Lin Z, Yin P, et al. Differential expression of microRNA species in human uterine leiomyoma versus normal myometrium. Fertil Steril. 2008;89(6): 1771–6.
73. Ono M, Yin P, Navarro A, et al. Paracrine activation of WNT/β-catenin pathway in uterine leiomyoma stem cells promotes tumor growth. Proc Natl Acad Sci U S A. 2013;110(42):17053–8.
74. Karra L, Shushan A, Ben-Meir A, et al. Changes related to phosphatidylinositol 3-kinase/Akt signaling in leiomyomas: possible involvement of glycogen synthase kinase 3alpha and cyclin D2 in the pathophysiology. Fertil Steril. 2010;93(8):2646–51.
75. Varghese BV, Koohestani F, McWilliams M, et al. Loss of the repressor REST in uterine fibroids promotes aberrant G protein-coupled receptor 10 expression and activates mammalian target of rapamycin pathway. Proc Natl Acad Sci U S A. 2013;110(6):2187–92.
76. Marret H, Fritel X, Ouldamer L, et al. Therapeutic management of uterine fibroid tumors: updated French guidelines. Eur J Obstet Gynecol Reprod Biol. 2012;165(2):156–64.
77. Di Fazio P, Montalbano R, Neureiter D, et al. Downregulation of HMGA2 by the pan-deacetylase inhibitor panobinostat is dependent on hsa-let-7b expression in liver cancer cell lines. Exp Cell Res. 2012;318(15):1832–43.
78. Pejić S, Kasapović J, Todorović A, et al. Lipid peroxidation and antioxidant status in blood of patients with uterine myoma, endometrial polypus, hyperplastic and malignant endometrium. Biol Res. 2006;39(4): 619–29.
79. El Ayed M, Bonnel D, Longuespée R, et al. MALDI imaging mass spectrometry in ovarian cancer for tracking, identifying, and validating biomarkers. Med Sci Monit. 2010;16(8):BR233–45.
80. Franck J, Arafah K, Elayed M, et al. MALDI imaging mass spectrometry: state of the art technology in clinical proteomics. Mol Cell Proteomics. 2009;8(9): 2023–33.

Uterine Myomas and Histopathology

3

Leonardo Resta

Introduction

The uterine leiomyoma or fibroid is one of the most common tumours in females, mostly asymptomatic, with an incidence of 22–77 %, typically occurring in the fourth and fifth decade of life, perhaps related to the general changes in the hormonal regime at this age. Recent genetic analysis has associated variants in BET1L and TNRC6B with the volume of leiomyomata [1]. Associations with African ethnicity, with the levels of per oestrogen and progesterone receptors, with regulatory mechanisms and their metabolism, and vitamin D deficiency have all been studied [2]. The correlation with the onset of menarche also seems important as each year of its delay is inversely correlated with the number and size of the tumours [3]. Symptoms are related to the number and size of the lesion: a sense of heaviness, compression of near organs and bleeding.

In 65–70 % of cases leiomyomata are multiple and can be found in various locations most frequently within the wall of the uterus where they can expand in the myometrium (Intramural leiomyoma), beneath the endometrium, simulating a polyp (submucosal leiomyoma), beneath the serosal surface (subserosal leiomyoma), within the broad ligament, simulating an adnexal neoplasia (infraligamentous leiomyoma) or at the isthmus or the miometrium of the neck (cervical leiomyoma). The compression of the endometrium causes atrophy and erosion with bleeding. Subserosal leiomyomata can be pedunculated and in some cases can separate from the uterus and create a new vascular pedunclе with another nearby organ (parasitic leiomyoma).

They are well circumscribed, firm, grey-white and with a whorled cut surface. They may degenerate, especially in pregnancy, and become soft with a yellowish hue in necrosis or a reddish colour due to haemorrhaging.

Histologically (Fig. 3.1), the tumour is made up of cells similar to that of the contiguous endometrium (elongated, eosinophilic cytoplasm with central, blunt-ended, pale elongated nucleus, sometimes with clumped chromatin. The cells form whirling fascicles interlaced at right angles. This arrangement clearly distinguishes the leiomyoma from the surrounding myometrium, which shows a more regular pattern of the muscle fibres. Furthermore, a large number of tumours show a clear border with the myometrium, even forming a valley, exaggerated by fixation artefact, with the formation of a ring of compressed myometrial cells (Fig. 3.2). In conservative myomectomy the surgeon exploits this valley to allow an easy excision of the tumour from the uterine wall. This interstitial space is

L. Resta, MD
Department of Emergency and Organ Transplantation (DETO), Section of Pathological Anatomy, University of Bari, Italy
e-mail: leonardo.resta@uniba.it

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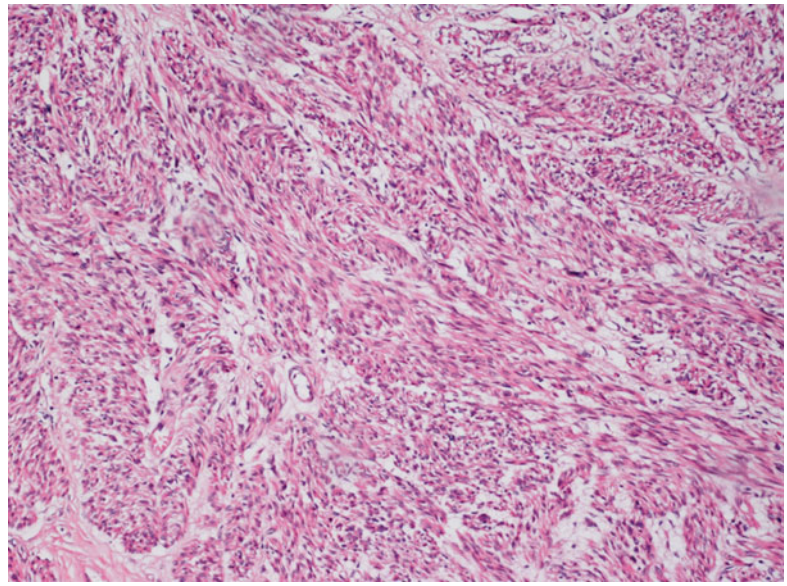

Fig. 3.1 A typical uterine leiomyoma, composed by bundles of spindle cells, similar to those present in the myometrial wall: only the whirling and irregular arrangement of the cellular bundles distinguish the neoplastic proliferation. The large and ribbon-like eosinophilic cytoplasm is evident also at low magnification. In the present picture, a small amount of hyaline connective tissue is organized around the arterial vessels and among the cellular fascicles

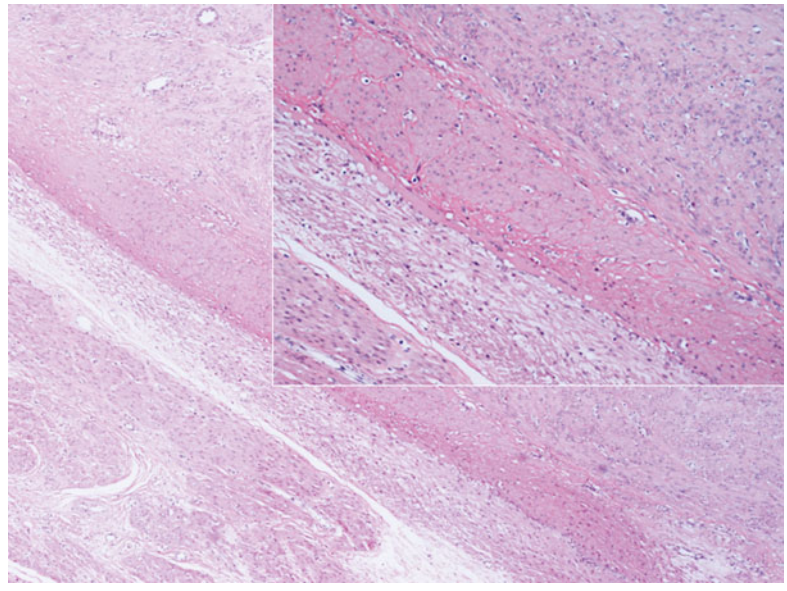

Fig. 3.2 Most of benign uterine leiomyomas shows defined margins as respect to the normal myometrium. The compression of normal smooth cells around the tumor forms a "pseudocapsule" from which the surgeon delivers the mass during the myomectomy. In insert image, a more accurate observation of the tumoral margins puts in evidence a layer of small compressed native smooth cells. The nuclei of these cells are not regressive: we can conclude that the "pseudocapsule" is an active form of contrast against the tumoral growth

formed from a variable amount of connective tissue (increasing with age and the menopausal state), possible oedema (Fig. 3.3) and many blood vessels of diverse calibre (Fig. 3.4).

Leiomyomata variants have differences that can be macroscopic or histological and thereby pose a serious problem of differential diagnosis with leiomyosarcoma.

First of all, there can be "infarct-type" necrosis or hyaline necrosis according to Bell et al. [4], characterized by areas of seemingly coagulative necrosis separated from the rest of the tumour by rings of fibrous or granulation tissue (Fig. 3.5). This type of necrosis must not be confused with "tumour cell necrosis" observed in leiomyosarcoma where the cells are pervasively necrotic,

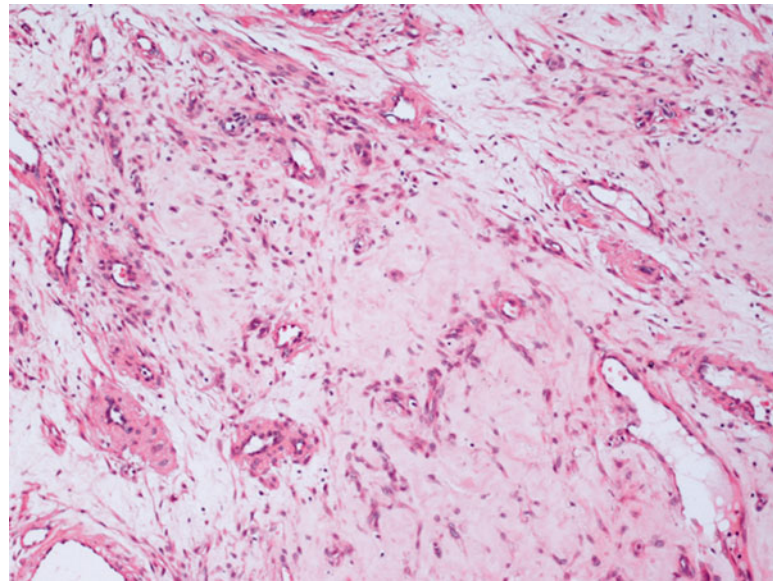

Fig. 3.3 A leiomyoma with a diffuse interstitial oedema. In this area, an otherwise typical uterine leiomyoma, shows few neoplastic cells merged with a large amount of loose interstitium and several vessels. This pattern is different from that of the more dangerous myxoid leiomyioma

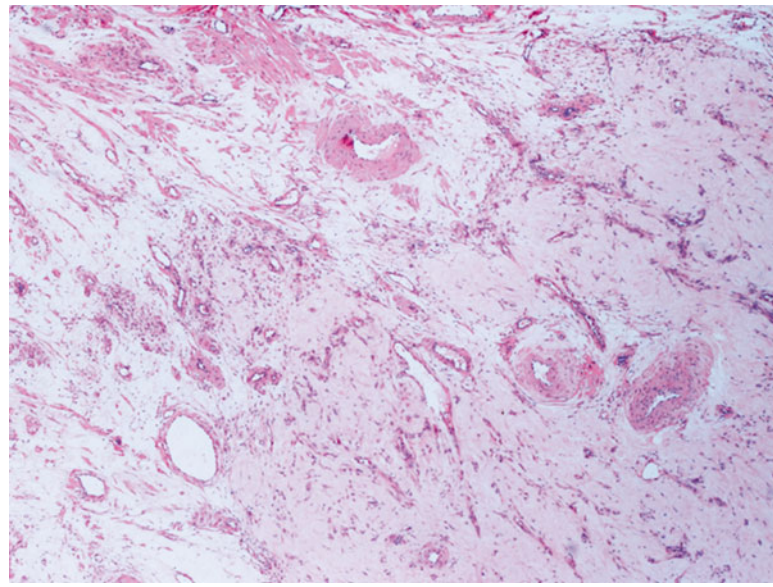

Fig. 3.4 The present uterine leiomyoma is provided of a great amount of vessels: arteries with thick muscular wall, large veins and capillary vessels. The stroma is very oedematous. The special conformation of the tumour (angioleiomyoma) may evocate different diagnosis with US or other instrumental examination

there is no separation from the surrounding tumour and often there are clumps of the residue of neoplastic cells surrounding residual vascular structures, commonly known as ghost outlines (Fig. 3.6).

The differential diagnosis with leiomyosarcoma supposes, other than "tumour cell necrosis", the presence of moderate-severe atypia and a mitotic index over 10/10HPF (Fig. 3.7): according to the Bell criteria of Bell et al. [4] the presence of two out of three of these paramenters is enough to diagnose leiomyosarcoma. Immunohistochemistry does not bring any further advantages to the differential diagnosis. The borders of the tumour often infiltrate the near myometrium without the presence of the

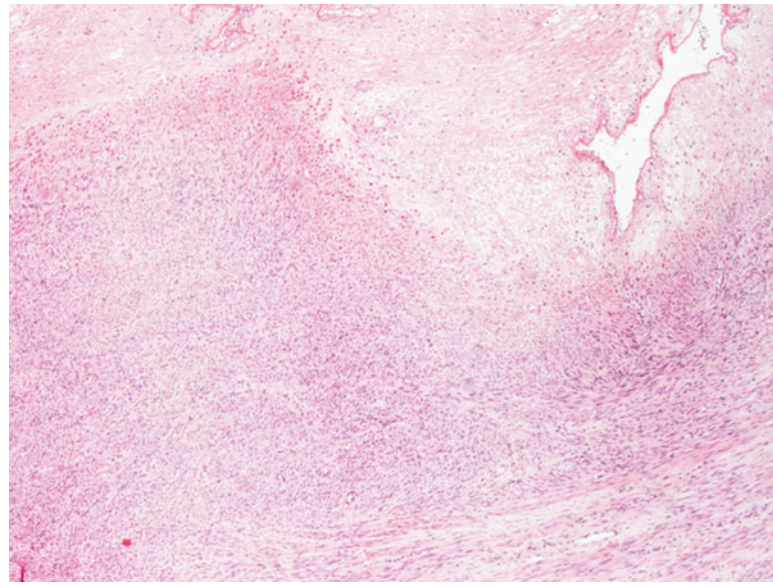

Fig. 3.5 A typical degenerative necrosis in an otherwise typical leyomioma. The regressive hypocellular area (*bottom*) is sharply limited from the neoplastic vital cells. No granulocyte infiltration is observed at the border of necrosis

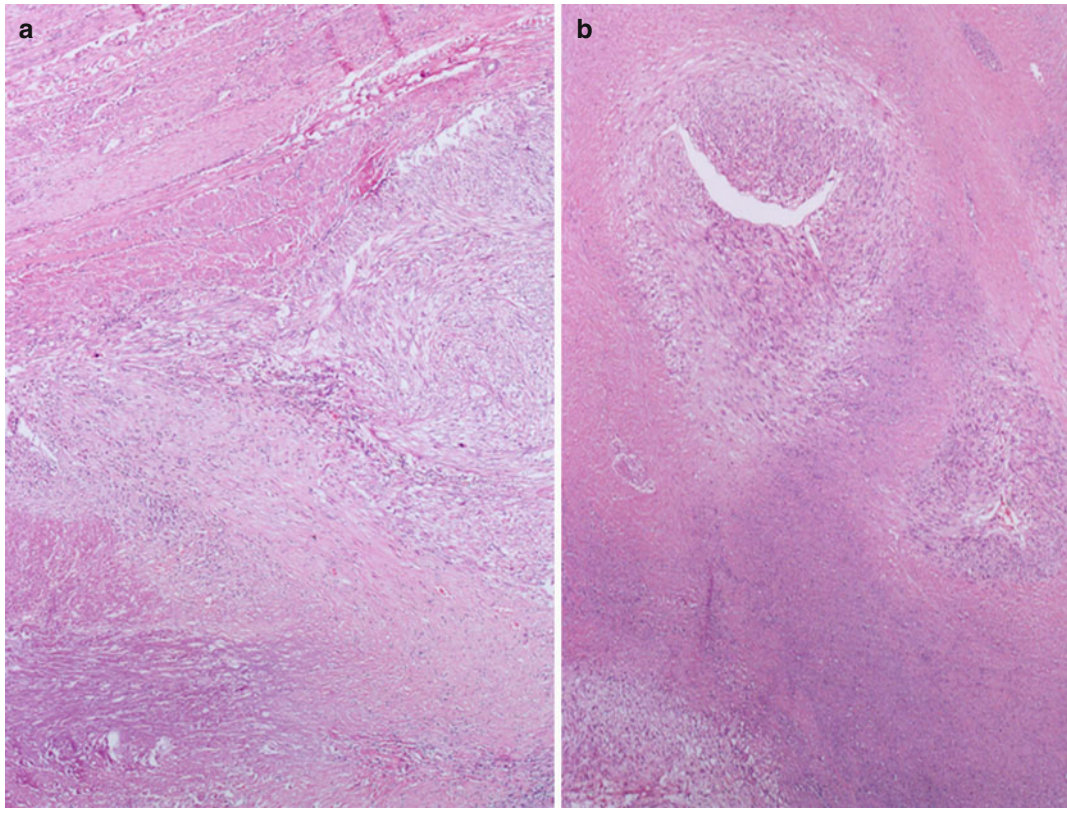

Fig. 3.6 In leiomyosarcoma is often present a particular form of necrosis named "tumoral necrosis". In this figure the necrosis is present in the lower part and it is separate from the vital cells by a layer of granulation tissue characterized by small vessels and infiltration of neutrophil granulocytes. Note the absence of the "pseudocapsule" between the tumor and the normal myometrium (on the *bottom*) (**a**). In a "tumoral necrosis" of a leiomyosarcoma the residual vital malignant cells are arranged as cellular poorly defined nodules around two arteries (**b**)

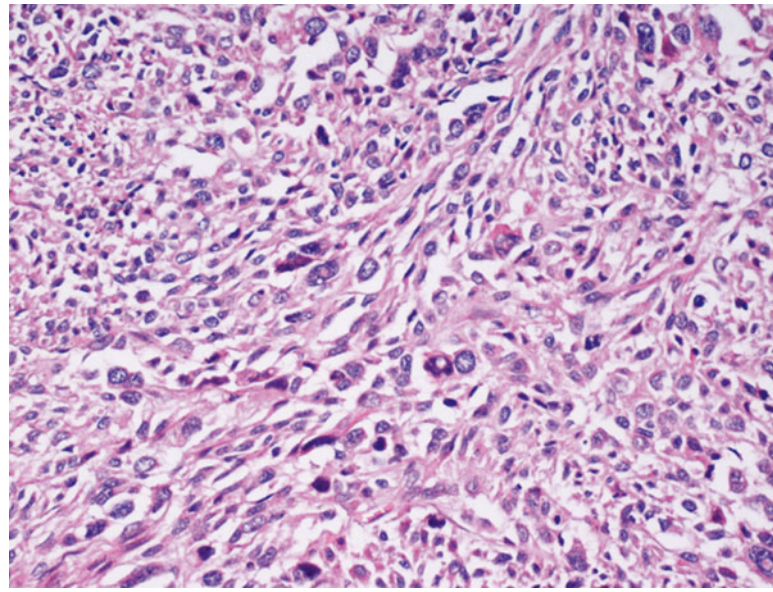

Fig. 3.7 In a malignant smooth muscle cell tumour of the uterus the cells maintain the spindle shape, but the nuclei are dysmetric, hyperchromatic, with rare evident eosinophilic inclusions. Mitoses, also of atypical aspect, are frequent

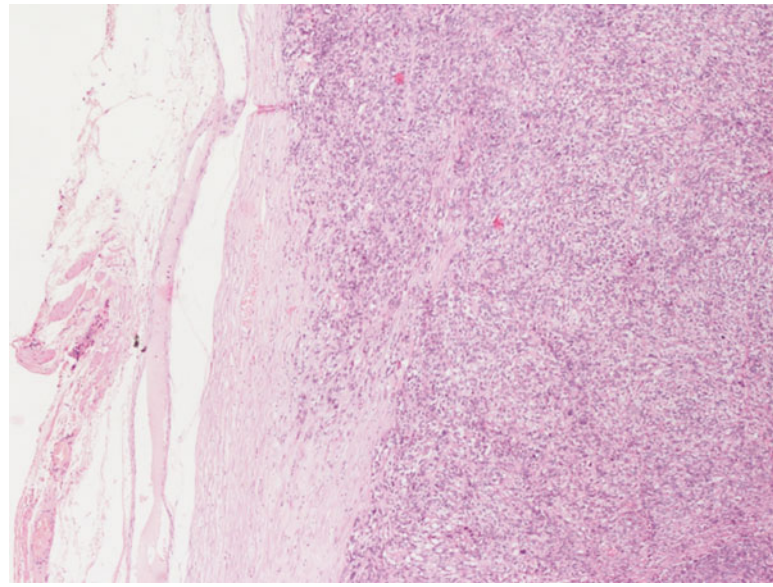

Fig. 3.8 At the margins of a leiomyosarcoma the "pseudocapsule" is always absent. The neoplastic cells invade the normal myometrium. In this case the peritoneal surface of the uterus (on the *left*) is obscured by a fibrous scar

pseudocapsule observed in benign leiomyomata (Fig. 3.8). Clearly malignant tumours express more p16, p21 and p53, but this is not helpful in single cases [5].

The expression of Ki 67 is also higher in leiomyosarcomas: in our experience Ki 67 is constantly higher than 40 %, while in leiomyomata it is always less than 10 %.

Necrosis can also be observed beneath the endometrium in tumours that grow into the uterine cavity which ulcerate and bleed, and therefore the necrotic cells are found together with inflammatory infiltrates.

Other degenerative changes, more of less common, are: *hyaline transformation* of the stroma (Fig. 3.9), leading to the wide substitution of the tumour, *dystrophic calcification* for a calcium salt deposition in the interstitial stroma (more common in menopausal women) (Fig. 3.10), a *hydropic degeneration* that can lead

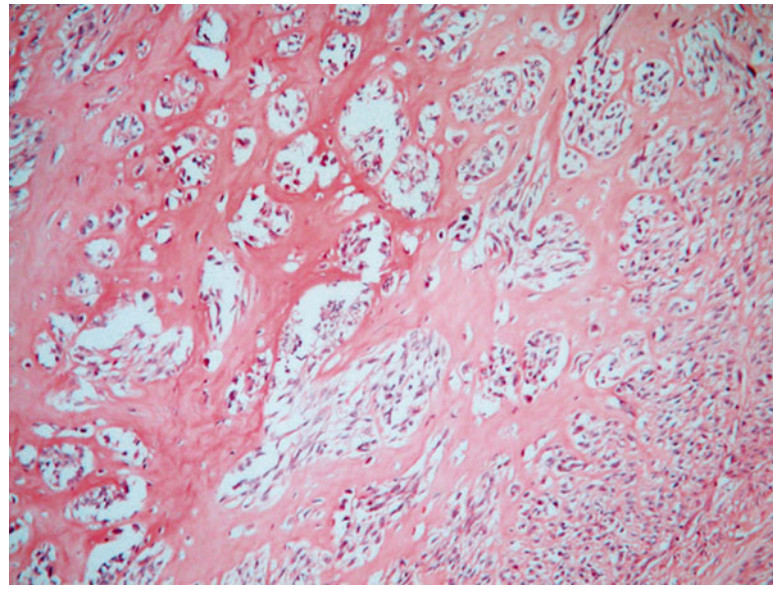

Fig. 3.9 A large part of the stroma in this usual leiomyoma is substituted by hyaline collagen. The neoplastic cells seem to be atrophic and compressed in small clusters

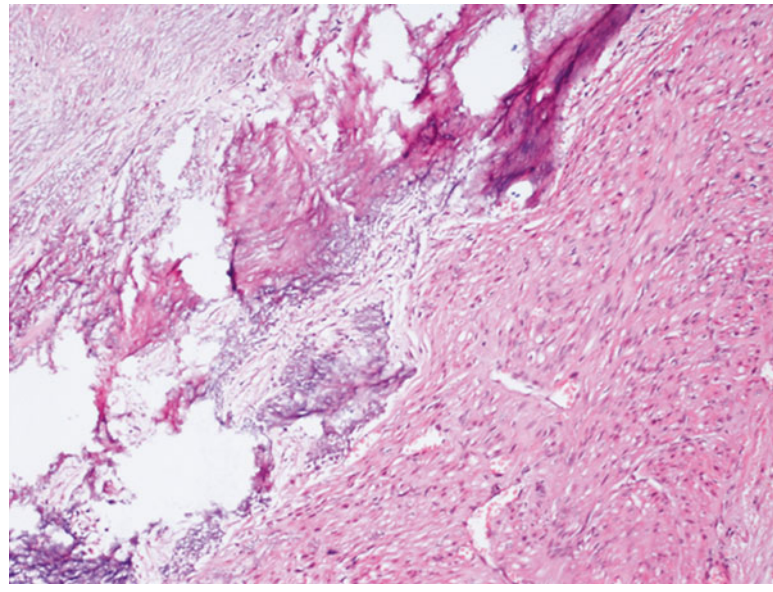

Fig. 3.10 Area of a typical leiomyoma with degenerative hyaline stroma with a subsequent dystrophic calcification and osseous metaplasia. This phenomenon may be focal or involving almost all the neoplasia, especially in perimenopausal women. Such tumours are evident at radiological examination

even to the formation of pseudocysts full of clear liquid.

A rarer but important type of change is myxoid degeneration (Fig. 3.11) of the fibroid when a gelatinous material is formed and the leiomuscolar cells can appear star-shaped and immersed in a slightly basophile stroma. Here the margins of the tumour must be closely examined as well circumscribed and the mitotic index is an essential point. A myxoid leiomyosarcoma, besides invading the surrounding miometrium, displays evident mitotic figures with only 2 per 10 HPF necessary to presume a malignant behaviour.

During pregnancy, leiomyomata can undergo necrosis and suffer bleeding (red degeneration), depending on the hormonal situation. Similar degeneration has been seen in hormonal therapy with estroprogestins. GnRH – analogue therapy

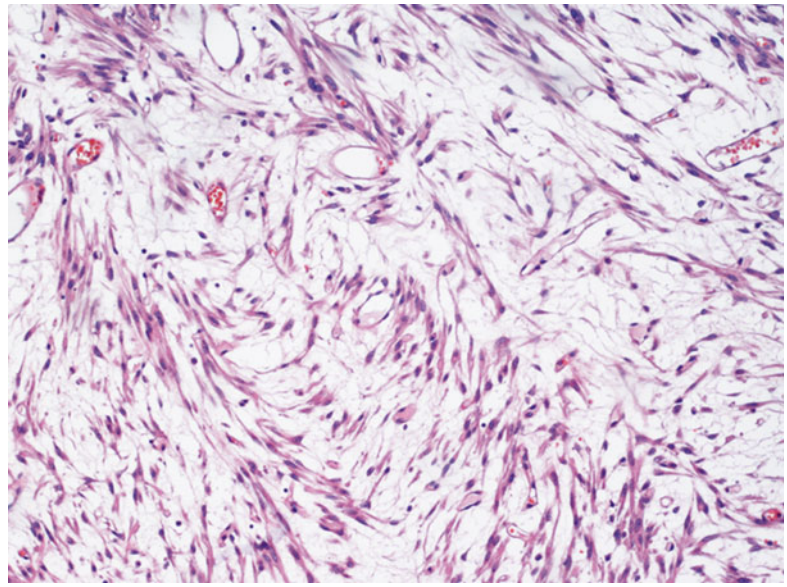

Fig. 3.11 In a myxoid leiomyoma the tumoral spindle cell are dispersed in a basophilic stroma. Several cells assume a stellate form. The diagnosis of this tumour is clinically relevant because the presence of a few mitoses suggests an aggressive behaviour

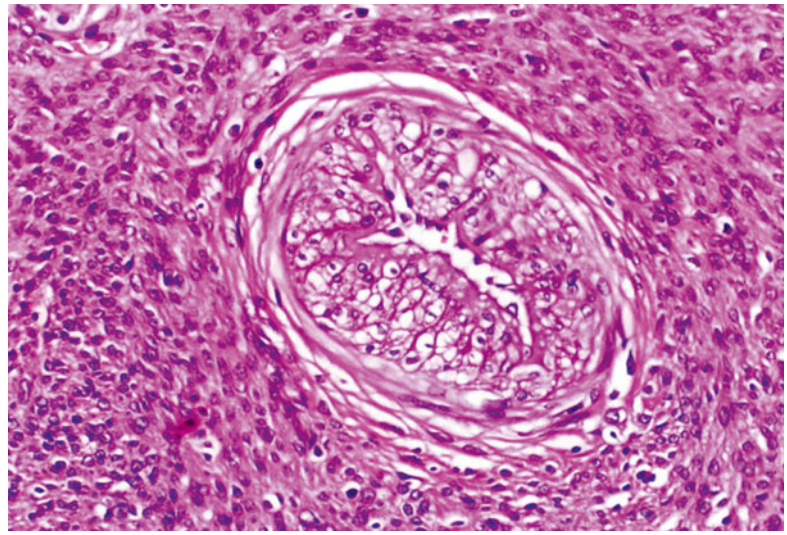

Fig. 3.12 Uterine leiomyoma treated with GhRH analogue for 3 months. Neoplastic cells are smaller and provided of large nucleus and scant cytoplasm, with a pseudo "cellular" pattern. The arterial wall is tick and rich in proliferating smooth muscle cells of the tunica media, with vacuolated cytoplasm. The lumen is narrowed

causes a high degree of cellularity of the tumour which can confuse the pathologist when analyzing the mitotic figures. The increase in cellularity is apparently an effect linked to cell atrophy which reduces the cytoplasm thickness with closer nuclei, often with densely packed chromatin. As we discussed in a previous paper, the arteries we have described alterations of the inner wall (Fig. 3.12) coherent with the proliferation of muscle cells and distortion or restriction of the lumen [6].

Particular Types of Leiomyomata

Cellular leiomyoma (Fig. 3.13) has increased cellularity and the cells are more densely packed than the surrounding myometrium. Macroscopically they are softer and pinker than the usual leiomyoma, though retaining a distinct border. There can occasionally be necrotic areas with multinuclear cells and haemorrhaging. Microscopically, cells are in mutual contact, with less cytoplasm, an ellipsoidal nucleus, without

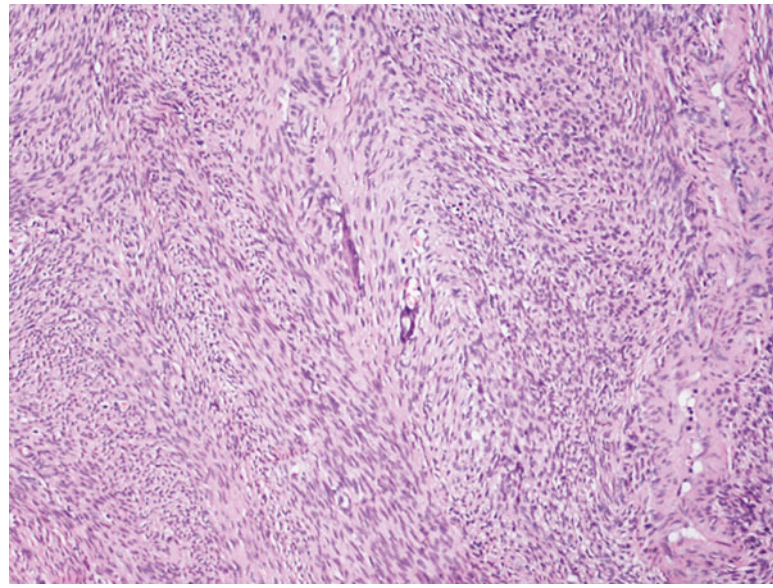

Fig. 3.13 Cellular leiomyoma. The cells are more numerous than in a typical leiomyoma, but the spindle shape of cells and the architecture of bundles are preserved. The nuclei are more frequent in reason of the smaller size of the cells. On the right, a large artery shows an evident muscular wall connected with tumoral proliferative cells

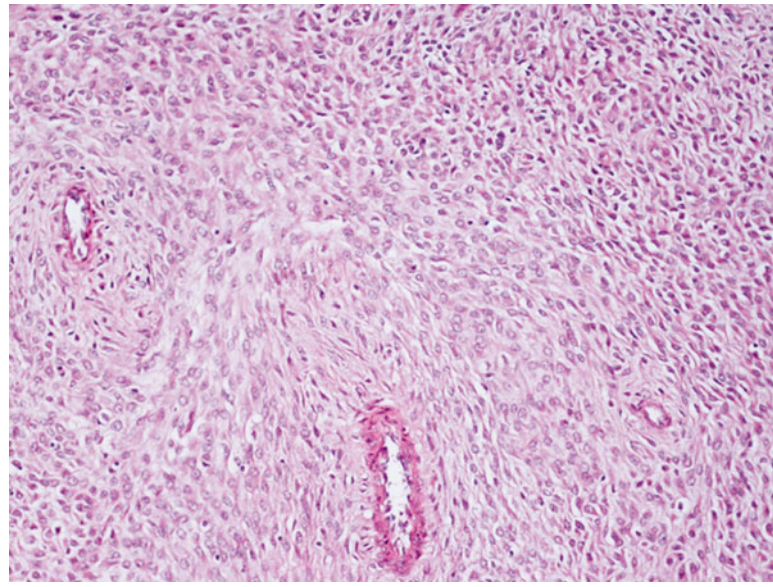

Fig. 3.14 At higher magnification, a cellular leiomyoma shows a typical aspect of the arterial vessels: an evident thick wall, in which the muscular cells seems to generate the cell of the tumor. On the contrary, the arteries of the low grade endometrial stromal sarcoma are defined by a very thin muscular wall, similar to those observed in the proliferative endometrium

atypia and a low mitotic count. "Tumour type necrosis" is absent. In a recent re-evaluation of 76 cases by Rothmund et al. [7], there were no aggressive neoplasia indicated but only 6 recurrences in women who underwent uterus-conserving surgery. Differential diagnosis with low-grade endometrial stromal sarcomas is difficult. The latter have often infiltration of the myometrium and/or the lymphatic vessels. The arteries have a thin muscular wall. A well circumscribed tumour, with thick-walled arteries, without vascular invasion points to a cellular leiomyoma (Fig. 3.14). Criteria based on the expression of smooth muscle actin and desmin in the leiomyomata and of vimentin and CD 10 in the stromal tumour can only confuse as exceptions are numerous.

Bizarre (or symplastic) leiomyomata (Fig. 3.15) usually have a standard appearance though they can have a yellowish colour and degenerative cystic areas. At a histological level they show bizarre multinucleated tumour cells

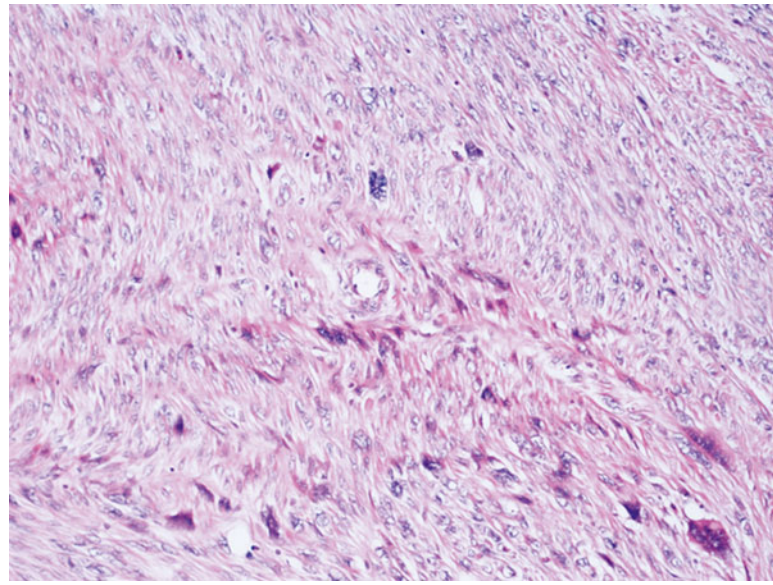

Fig. 3.15 In few uterine leiomyomas, a more or less extensive part is composed of large multinucleated cells. This kind of neoplasms is named "symplasmic or bizarre leiomyoma". The multinucleated cells show regressive hyperchromatic nuclei, different from usual kariorhessis. The absence of abnormal mitoses and necrosis exclude the diagnosis of leiomyosarcoma

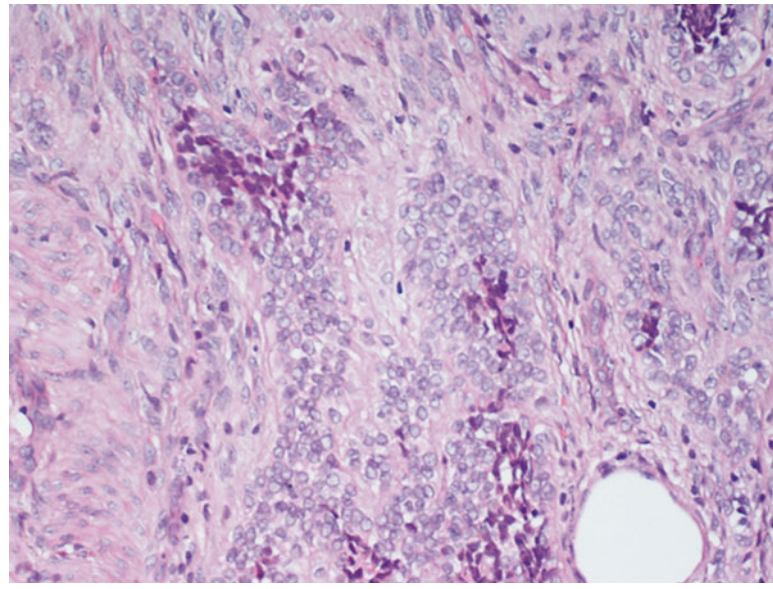

Fig. 3.16 A smooth cell tumor of the uterus with scanty cytoplasm shows an "epitheloid" pattern. Small clusters of this type of cells are named "plessiform tumorletts". If almost all the leyomioma is composed of epithelioid cells the risk of malignancy is a real possibility: few mitoses are sufficient for a diagnosis of "epithelioid leiomyosarcoma"

with dark, compact dysmetric nuclei. These cells can be found either in one part of the tumour or in more loci or be diffuse within the tumour. The low mitotic index and the lack of tumour cell necrosis excludes malignance. These cells, far from being aggressive, have a regressive aspect, perhaps of a vascular nature, and the compact and hyperchromatic appearance of the nucleus are evident signs of inactivity.

Mitotically active leiomyomata are fortunately rare, but difficult to diagnose [8]. They usually affect young patients often with a history of various types of hormonal stimulation. The mitotic index is elevated (usually below 20MF/10HPF). Leiomyosarcoma is excluded because of no cytological atypia, no tumour cell necrosis and no abnormal mitotic figures. Researchers do not agree if this tumour has a more rapid growth than a typical leiomyoma.

The **epithelioid leiomyoma** (previously also known as leiomyomblastoma) (Fig. 3.16) is an intriguing tumour which is formed from polygonal

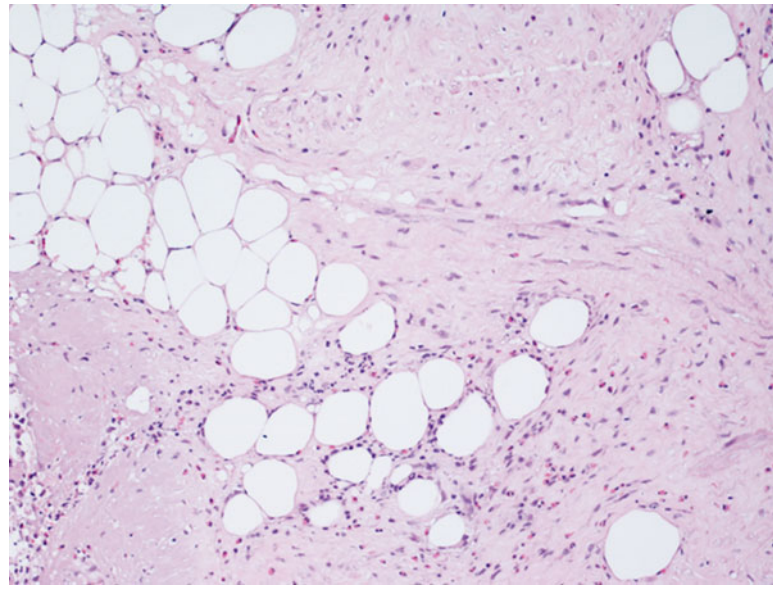

Fig. 3.17 This tumor presents a various amount of lipocytes within the normal smooth cells. A differential diagnosis with vessel swelling is mandatory. A pure lipoma of the uterus is of very rare occurrence. The presence of small lipocytes and perivascular lipoblasts justifies the theory of the origin of this cells from undifferentiated stromal cells

cellular elements, with a mainly clear cytoplasm, joined together in ribbons or islands. The epithelioid form is due to the positivity of the cytokeratin and the negativity of the muscle antigens. Close observation of many parts of the tumour shows a transition toward more characteristic ellipsoidal shaped cells. Here even a low mitotic count (2–4 MF/10HPF) is indicative of a malignant tumour. In these cases the tumour borders are frequently of the invasive type.

The **intravenous leiomyoma** grows within the veins, but does not show malignant characteristics being without cytologic atypia, high mitotic index of necrotic loci. They can cause peritoneal or pulmonary metastases, though these can also occur with completely typical leiomyomata.

Like the leiomyoma, the **lipoleiomyoma** (Fig. 3.17) is also a benign, well defined mass but has a high content of adipose tissue. They are frequent in older women and therefore could be a consequence of fatty degeneration or metaplasia of smooth muscle cells. However we must not underestimate the possibility of an activation of fibroblasts with staminal characteristics as seen in a perivascular location [9].

The presence of adipocytes among myocytes cannot be confused with vascular ectasia which is always possible especially in voluminous tumours or those with microcystic spaces lined by flattened or cuboidal cells as seen in adenomatoid tumours. These are benign peritoneal tumours of mesothelial origin which grow between the cells of a leiomyoma in the walls of the uterus. A cytokeratin or vimentin can reveal the nature of the clear intercellular spaces (Fig. 3.18).

Metastazing leiomyoma (Fig. 3.19) is considered a smooth muscle tumour of the uterus which is able to reproduce in other organs (especially pelvic lymph nodes or lung) without evident signs of malignancy (absence of high mitotic rate, necrosis and cellular atypia). The presence of an unknown intravenous tumoral growth is a possible hypothesis. This diagnosis is performed only after a careful examination of the uterine tumour, in order to exclude a low grade leiomyosarcoma. The expression of hormonal receptor does not exclude a pulmonary primitive proliferation of smooth muscle cells.

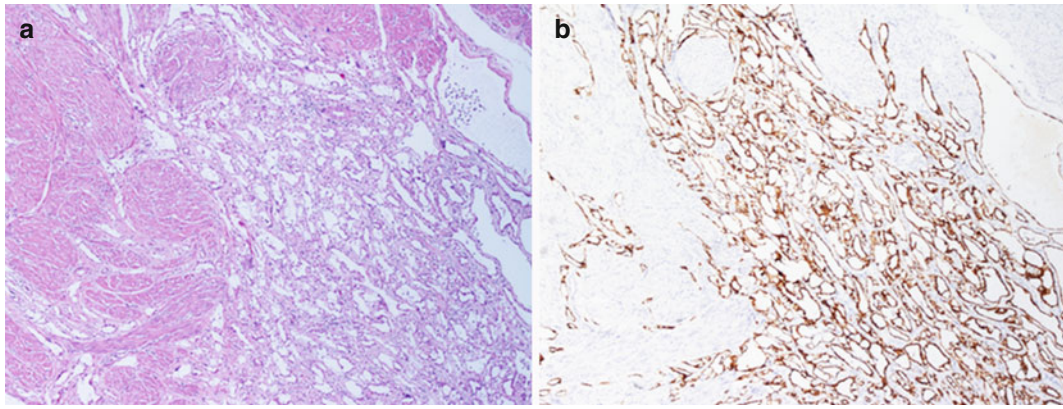

Fig. 3.18 In few typical uterine leiomyomas, we can find a lot of clear spaces lined by flat or occasional cuboidal cells. This phenomenon is the result of an integration of two neoplasms: a leiomyoma and an adenomatoid tumor (a benign proliferation of the mesothelium) (**a**). This pattern needs to be differentiated from lipoleiomyoma or a leiomyoma with lymphatic vessel dilatation. The immunohistochemistry is essential in the differential diagnosis. In the picture the same area is tested with cytokeratins which are strong expressed by adenomatoid tumor (**b**)

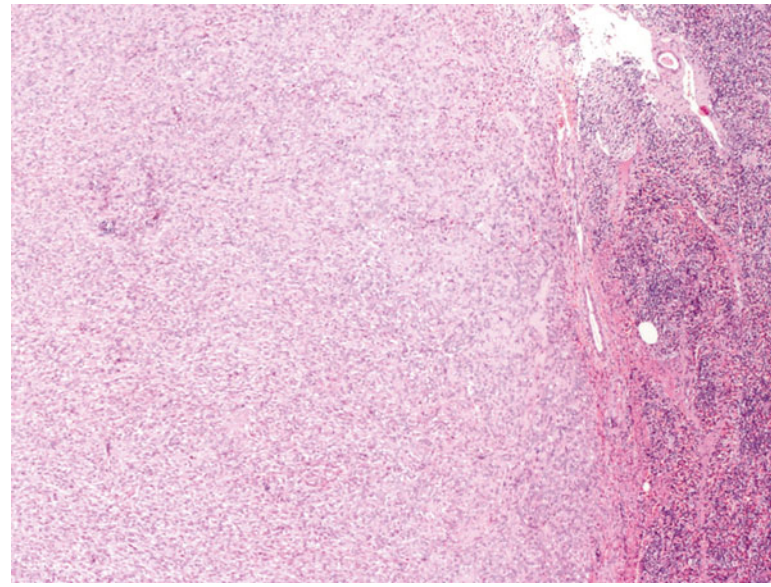

Fig. 3.19 A "metastasizing leiomyoma" observed in a pelvic lymph node. The lymphoid tissue is evident on the right side of the picture. The aspect of the proliferating leiomyoma is usual and no necrosis is present. The positivity at MIB1 is less than 2 %

STUMP

The differential diagnosis between leiomyoma e leiomyosarcoma is not always easy. The Bell criteria (evident atypia, tumour cell necrosis and high mitotic count) are not always all present, rather, according to Bell et al. [4], 2 criteria in 3 are sufficient. In some cases the criteria are vague and the diagnosis is problematic (Fig. 3.20). These borderline tumours are known as STUMP, smooth muscle tumour of undetermined malignant potential. Some authors think that there is overlap between this category and other categories of atypical leiomyomata [10]. Today it is

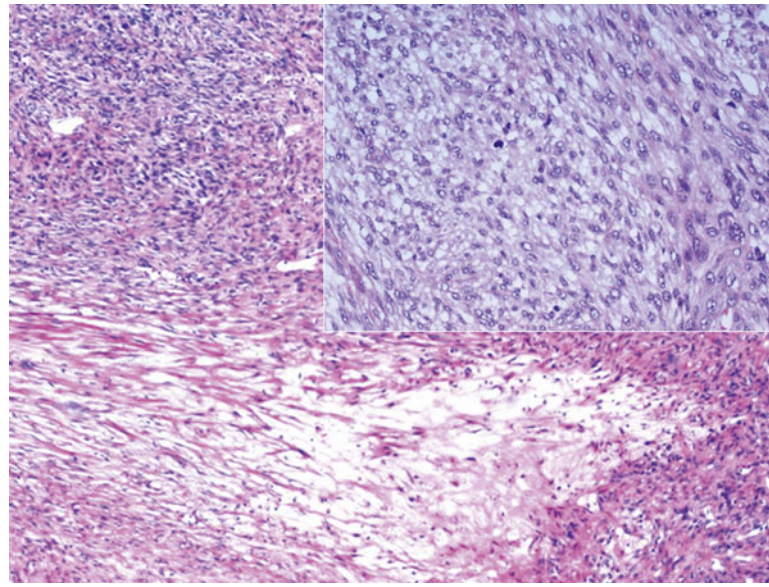

Fig. 3.20 This uterine tumour is composed by smooth muscle cells, and presents high cellularity, small areas of not well defined necrosis, and a mitotic rate (in the insert picture) of 8/10 HPF. A diagnosis of STUMP has been made

thought that it is likely that these tumours are not simply diagnostic uncertainties but are neoplasia which can relapse after several years and which are less aggressive than leiomyosarcomas [11].

References

1. Edwards TL, Michels KA, Hartmann KE, Velez Edwards DR. BET1L and TNRC6B associate with uterine fibroid risk among European Americans. Hum Genet. 2013;132(8):943–53.
2. Catherino WH, Eltoukhi HM, Al-Hendy A. Racial and ethnic differences in the pathogenesis and clinical manifestations of uterine leiomyoma. Semin Reprod Med. 2013;31(05):370–9.
3. Velez Edwards DR, Baird DD, Hartmann KE. Association of age at menarche with increasing number of fibroids in a cohort of women who underwent standardized ultrasound assessment. Am J Epidemiol. 2013;178(3):426–33.
4. Bell SW, Kempson RL, Hendrickson MR. Problematic uterine smooth muscle neoplasms: a clinicopathologic study of 213 cases. Am J Surg Pathol. 1994;18:535–58.
5. Kobayashi H, Uekuri C, Akasaka J, Ito F, Shigemitsu A, Koike N, Shigetomi H. The biology of uterine sarcomas: a review and update. Mol Clin Oncol. 2013;1(4):599–609.
6. Resta L, Sanguedolce F, Orsini G, Laricchia L, Piscitelli D, Fiore MG. Morphometric and histological evaluation of GnRH agonists or progestational agents-treated uterine leiomyomas. Pathologica. 2004;96:35–41.
7. Rothmund R, Kurth RR, Lukasinski NM, Huebner M, Hartkopf A, Wallwiener M, Staebler A, Brucker SY, Taran FA. Clinical and pathological characteristics, pathological reevaluation and recurrence patterns of cellular leiomyomas: a retrospective study in 76 patients. Eur J Obstet Gynecol Reprod Biol. 2013;171(2):358–61.
8. Prayson RA, Hart WR. Mitotically active leiomyomas of the uterus. Am J Surg Pathol. 1992;97:14–20.
9. Resta L, Maiorano E, Piscitelli D, Botticella MA. Lipomatous tumors of the uterus. Clinico-pathological features of 10 cases with immunocytochemical study of histogenesis. Pathol Res Pract. 1994;190(4):378–83.
10. Deodhar KK, Goyal P, Rekhi B, Menon S, Maheshwari A, Kerkar R, Tongaonkar HB. Uterine smooth muscle tumors of uncertain malignant potential and atypical leiomyoma: a morphological study of these grey zones with clinical correlation. Indian J Pathol Microbiol. 2011;54(4):706–11.
11. Ip PP, Cheung AN, Clement PB. Uterine smooth muscle tumors of uncertain malignant potential (STUMP): a clinicopathologic analysis of 16 cases. Am J Surg Pathol. 2009;33(7):992–1005.

Uterine Fibroids: Clinical Features

4

William H. Parker

Introduction

In the US, fibroids are estimated to cost $5.9–34.4 billion annually: direct costs including surgery, hospital admissions, outpatient visits, and medications are estimated at $4.1–9.4 billion; time lost for work costs are $1.55–17.2 billion [1].

In Europe, the annual costs of surgical and non-surgical interventions were euro 212 million in Germany, euro 73 million in France and euro 53 million in England [2].

Fibroids are the most frequent indication for performing hysterectomies and accounted for 238,000 such procedures in the US in 2004 [3].

In comparison, only 30,000 myomectomies were performed that year.

Incidence

Fibroids are very common. Fine sectioning of uteri from 100 consecutive women who had a hysterectomy revealed fibroids in 77 % [4].

Screening of a random sample of women ages 35–49 by self-report, medical record review and sonography (Fig. 4.1) found that the incidence of fibroids by age 35 was 60 % among African-American women and 40 % for Caucasian women; by age 50, over 80 % of African-American women and 70 % of Caucasian women had fibroids [5].

Risk Factors

Although selection bias may limit current epidemiologic studies, a number of factors associated with an increased risk of fibroids have been determined. Increasing age is associated with an increased incidence of fibroids: 4.3 per 1,000 woman-years for 25–29 year-olds; 22.5 for 40–44 year-olds [6].

African-American women have an almost three times greater risk of having fibroids than Caucasian women, unrelated to other known risk factors [7].

African-American women also have fibroids develop at a younger age, and have more numerous, larger and more symptomatic fibroids [8]. First degree relatives of women with fibroids have a 2.5 times increased risk of developing fibroids [9].

Greater exposure to endogenous hormones, as found with early menarche (<10 years old) increases, and late menarche decreases, the risk of having uterine fibroids [10]. Fibroids are also smaller and less numerous in hysterectomy specimens (Fig. 4.2) from postmenopausal women, when endogenous estrogen levels are low [11].

Factors that increase overall lifetime exposure to estrogen, such as obesity, increase the

W.H. Parker, MD
Department of Obstetrics and Gynecology,
UCLA School of Medicine, Los Angeles, CA, USA
e-mail: wparker@ucla.edu

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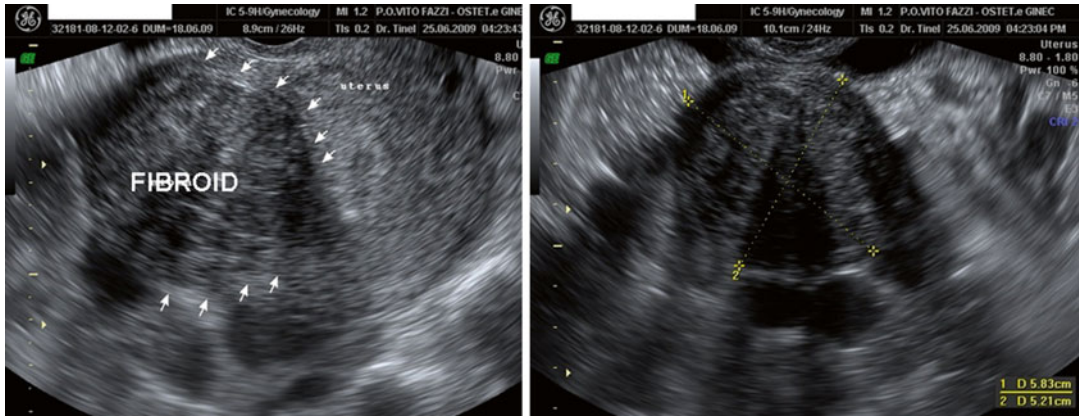

Fig. 4.1 Uterine sonography showing, on the *left*, an intramural fibroid and, on the *right*, a pedunculated fibroid

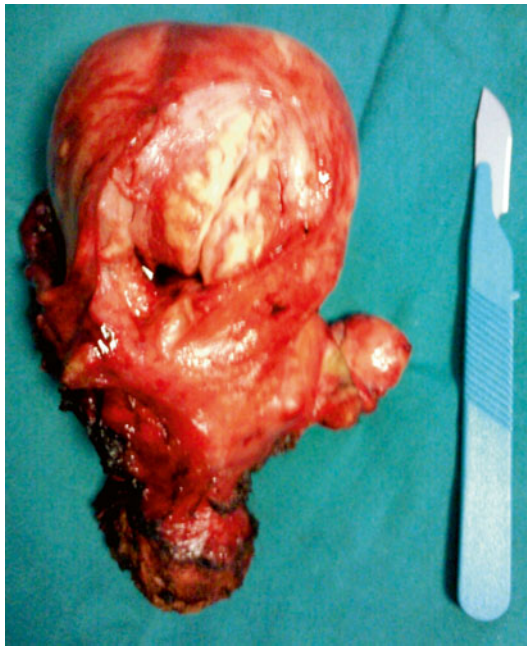

Fig. 4.2 Photo of uterus removed via colpohysterectomy with opening of the anterior uterine wall and a single fibroid appearing

incidence. Decreased exposure to estrogen found with smoking, exercise, and increased parity is protective [12].

In women with and without clinically detectable fibroids, serum levels of estrogen and progesterone are similar. However, aromatase within fibroids leads to denovo production of estradiol with higher levels than in normal myometrium. Fibroids have increased concentrations of progesterone receptors A and B compared with normal myometrium and the highest mitotic counts in fibroids are found at peak progesterone production, suggesting that progesterone influences fibroid growth [13–15].

Oral contraceptives do not increase the presence or growth of fibroids (Fig. 4.3) [16].

One study found an increased risk of fibroids with oral contraceptives [17], but a subsequent study found no increased risk with use or duration of use [18].

Although another study found a decreased risk [19], women with known fibroids may be prescribed oral contraceptives less frequently, leading to selection bias [20].

For the majority of postmenopausal women with fibroids, hormone therapy will not stimulate fibroid growth (Fig. 4.4).

If fibroids do grow, the progesterone is likely to be the cause (Fig. 4.5).

Among postmenopausal women with fibroids given 2 mg of oral estradiol and 2.5 or 5 mg of medroxyprogesterone acetate (MPA) daily for 1 year, 77 % percent of women on the lower dose of MPA had either no change or a decrease in fibroids diameters while 50 % of women taking 5 mg MPA had an increase in fibroid size [21].

Postmenopausal women with known fibroids, followed with sonography for 12 months, were

Fig. 4.3 A gynecological consultation of a patient worried to have uterine fibroids, after taking the oral contraceptive for a long time

noted to have an average 0.5 cm increase in the diameter of fibroid after using transdermal estrogen patches plus oral progesterone, but women taking oral estrogen and progesterone had no increase in size [22].

Increasing parity decreases the incidence and number of clinically apparent fibroids [23–25]. The remodeling of the postpartum myometrium, including apoptosis and dedifferentiation, may lead to involution of fibroids [26].

Alternatively, vessels supplying fibroids (Fig. 4.6) may regress during post-partum involution, depriving fibroids of their source of nutrition [27].

Obesity increases conversion of adrenal androgens to estrone and decreases sex hormone binding globulin, with an increase in biologically available estrogen. The risk of fibroids increases 21 % with each 10 kg increase in body weight, with increasing BMI and with greater than 30 % body fat. Few studies have examined the association between diet and the presence or growth of fibroids. One study found that red meat and ham increased the incidence of fibroids, while green vegetables decreased this risk, however, calorie and fat intake were not measured [28].

Women in the highest category of physical activity (approximately 7 h/week) were significantly less likely to have fibroids than women in the lowest category (<2 h/week) [29].

Smoking reduces the incidence of fibroids: nicotine inhibits aromatase and reduces conversion of androgens to estrone [30] and it leads to higher levels of SHBG, which decreases bioavailability of estrogen [31].

Clinical Presentation

Fibroids can cause morbidity and affect quality-of-life; women having hysterectomies due to fibroid-related symptoms (Fig. 4.7) have significantly worse scores on SF-36 quality-of-life questionnaires than women with hypertension, heart disease, chronic lung disease or arthritis [32].

Because the association of fibroids with heavy menstrual bleeding has not been clearly established, it is important to consider other possible etiologies including coagulopathies such as von Willebrandt's disease [33].

One study found that women with fibroids used 7.5 pads or tampons on the heaviest day of bleeding compared with 6.1 pads or tampons used by women without fibroids. Women with fibroids larger than 5 cm (Fig. 4.8) had slightly more gushing and used about three more pads or tampons on the heaviest day of bleeding than women with smaller fibroids [34].

A recent study reported that 259 women found to have submucous fibroids on hystero-

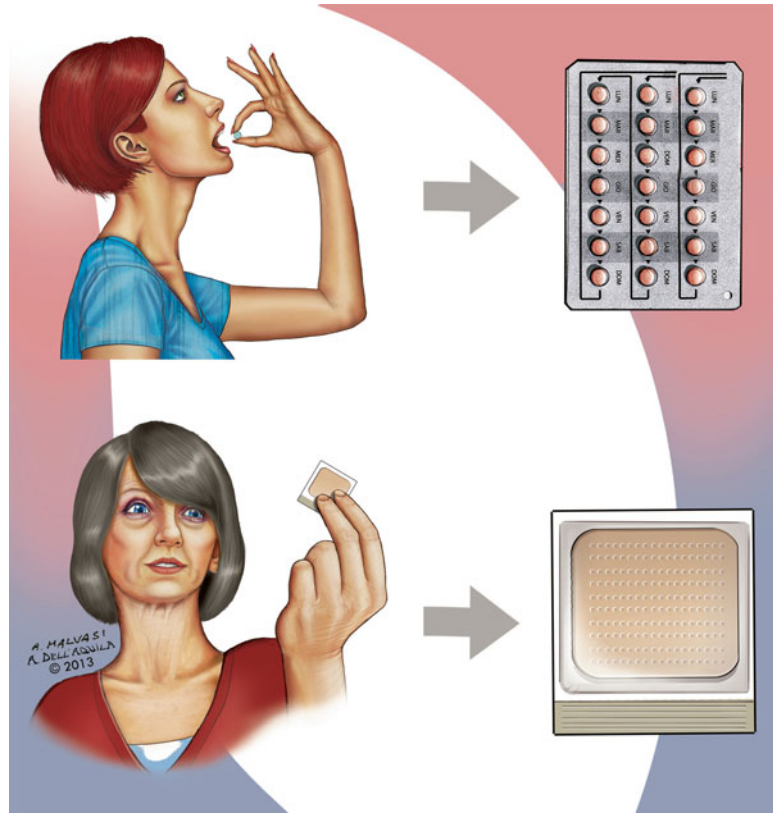

Fig. 4.4 A postmenopausal women assuming hormone replacement therapy in pills or in patch: they will not stimulate fibroid growth

scopic examination had objective measures of heavy menstrual bleeding, i.e., lower hemoglobin levels and a higher risk of anemia than women without submucous fibroids, although self-reported pictorial blood loss assessment did not differ. Women with fibroids are only slightly more likely to experience pelvic pain than women without fibroids. In one study, 96 women found to have fibroids based on transvaginal sonography reported moderate or severe dyspareunia or non-cyclic pelvic pain only slightly more than women without fibroids; there was no difference in moderate or severe dysmenorrhea. A study of 827 women with ultrasound detected fibroids found that deep dyspareunia was related to fibroids and the relationship was even stronger for "severe deep dyspareunia" [35].

However, women who present to gynecologists for evaluation with fibroid-associated pain may be different than those in the general population. As fibroids enlarge, they may outgrow their blood supply with resulting cell death and degeneration. The type of degeneration, as hyaline, cystic, or hemorrhagic (Fig. 4.9), appears to be unrelated to the clinical symptoms [36]. Rarely, torsion of a pedunculated subserosal fibroid may occur and produce acute pelvic pain that requires surgical intervention [37].

Fibroids cause urinary symptoms, although few studies have examined this association. Following uterine artery embolization and a 35 % reduction in mean uterine volume, 68 % of women had great or moderate improvement in frequency and urgency [38].

Likewise, a 55 % decrease in uterine volume following 6 month treatment with GnRH-a lead to a decrease in urinary frequency, nocturia and urgency [39].

There were no changes in urge or stress incontinence as measured by symptoms or urodynamic studies. These findings may be related to decrease in uterine volume or other effects of GnRH treatment.

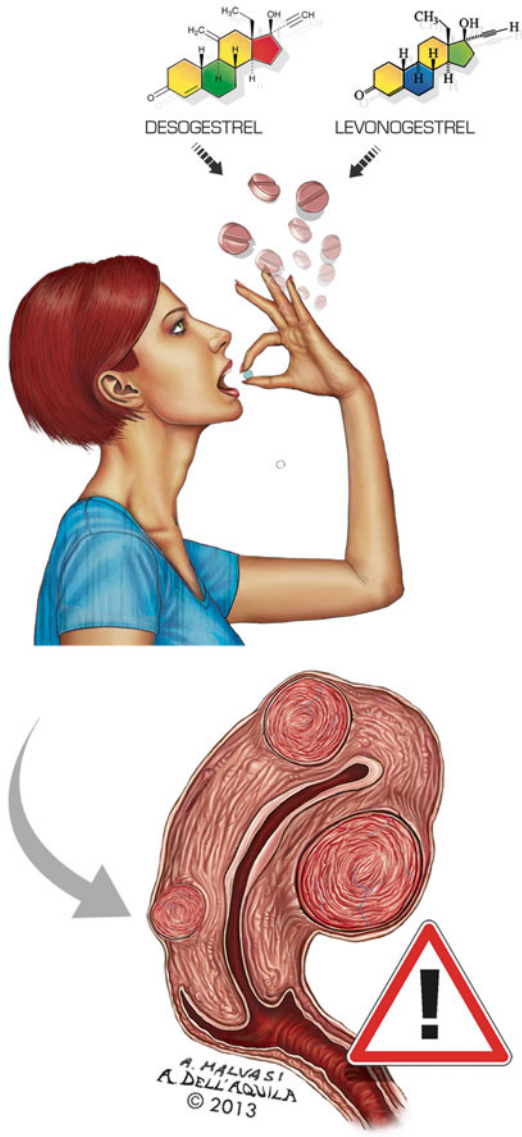

Fig. 4.5 A woman assuming progestins by oral pills: they can stimulate fibroid growth

Natural History of Fibroids

Predicting fibroid growth is not possible. Serial MRIs from 72 premenopausal women with fibroids found a median growth rate over 1 year of 9 % although 7 % of fibroids got smaller over the study period. The range of growth and shrinkage was very large: −89 to +138 % [6].

Small fibroids (<5 cm) had more frequent growth spurts than did larger fibroids. Surprisingly, multiple fibroids found in the same

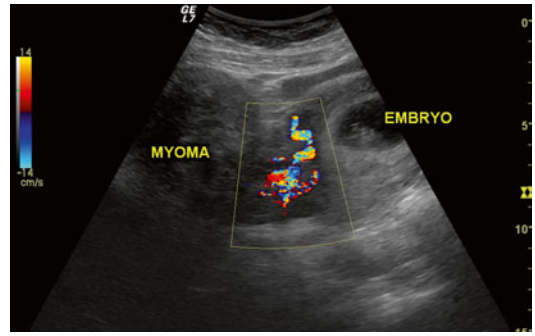

Fig. 4.6 Uterine sonography in early pregnancy showing, on the *left*, a uterine pedunculated myoma and, on the *right*, uterus with embryo

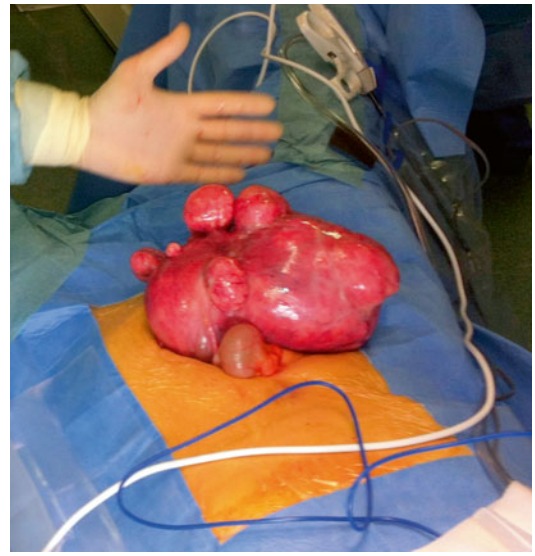

Fig. 4.7 A large fibroid uterus

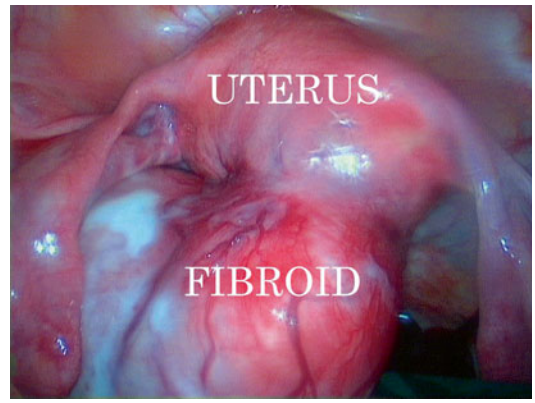

Fig. 4.8 A laparoscopic image of a non pregnant uterus with a posterior pedunculated fibroid of 8 cm of diameter

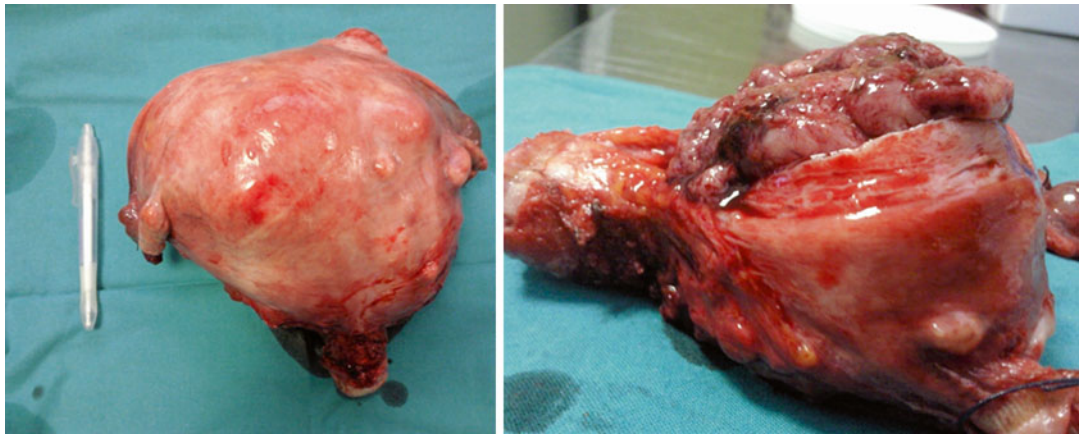

Fig. 4.9 A surgical image of a large myomatosic uterus on the *left*; on the *right*, the image shows a large fibroid in necrotic degeneration (with blood supply minimizing and resulting cell death and degeneration)

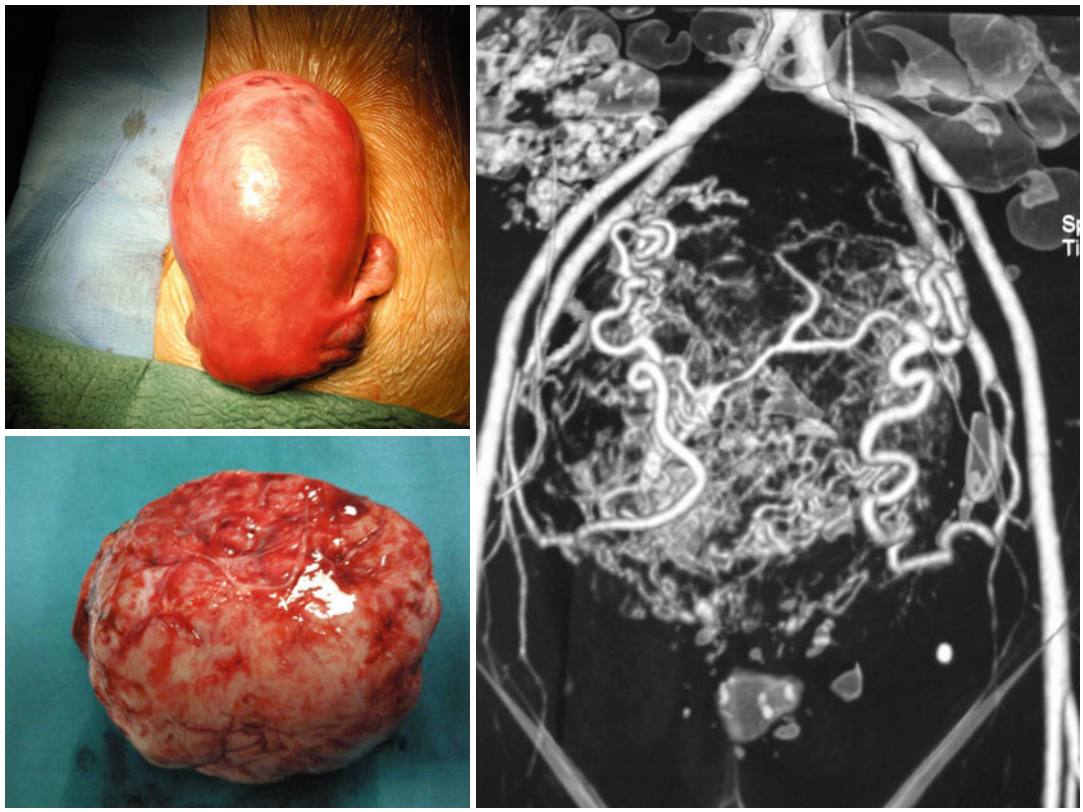

Fig. 4.10 A premenopausal women operated of abdominal hysterectomy for "rapid uterine growth": on the *top left*, the uterus with a fundal large fibroid; on the *right*, the angiographic image shows an hypervascularization of fibroids, with large supplying blood vessels; on the *lower left*, the single fibroid enucleated by pathologist

woman showed very variable growth rates, suggesting that a woman's hormone levels do not determine the rate of growth. After age 35, growth rates did not decline with age for black women, but did decline in white women. In premenopausal women, "rapid uterine growth" almost never indicates presence of uterine sarcoma (Fig. 4.10). One study found only 1 sarcoma

among 371 (0.26 %) women operated on for rapid growth of presumed fibroids [40]. No sarcomas were found in the 198 women who had a 6 week increase in uterine size over 1 year, one published definition of rapid growth. Women found to have uterine sarcoma are often clinically suspected of having a pelvic malignancy [41]. Between 1989 and 1999, the SEER database reported 2,098 women with uterine sarcomas with an average age of 63 years [42].

Genetic differences between fibroids and leiomyosarcomas indicate that leiomyosarcomas do not result from malignant degeneration of fibroids and comparative genomic hybridization did not find specific anomalies shared by fibroids and leiomyosarcomas [43].

In that fibroid growth is not predictable, women with fibroids who are mildly or moderately symptomatic, may choose to defer treatment. As women approach menopause and there is limited time to develop new symptoms, "watchful waiting" may be considered. There is no evidence that not having treatment for fibroids results in harm, except for women with severe anemia from fibroid-related heavy menstrual bleeding or hydronephrosis due to obstruction of the ureter(s) from an enlarged fibroid uterus (Fig. 4.11).

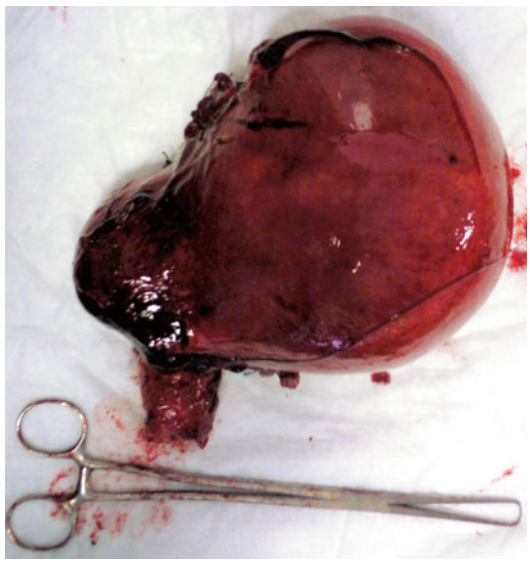

Fig. 4.11 An image of removed uterus by women with severe anemia: it shows an enlarged fibroid uterus, with related heavy menstrual bleeding and hydronephrosis due to obstruction of the left ureter

After 1 year of "watchful waiting", 77 % of women with uterine size 8 weeks or greater had no significant changes in the self-reported amount of bleeding, pain or degree of bothersome symptoms [44].

However, of the 106 women who initially chose "watchful waiting", 23 % opted for hysterectomy during the course of the year.

Diagnosis

Assessing uterine size by bimanual examination correlates well with uterine size and weight at pathological examination, even for most women with BMI >30 [45].

Transvaginal sonography (TVS) (Fig. 4.12), saline-infusion sonography (SIS), hysteroscopy,

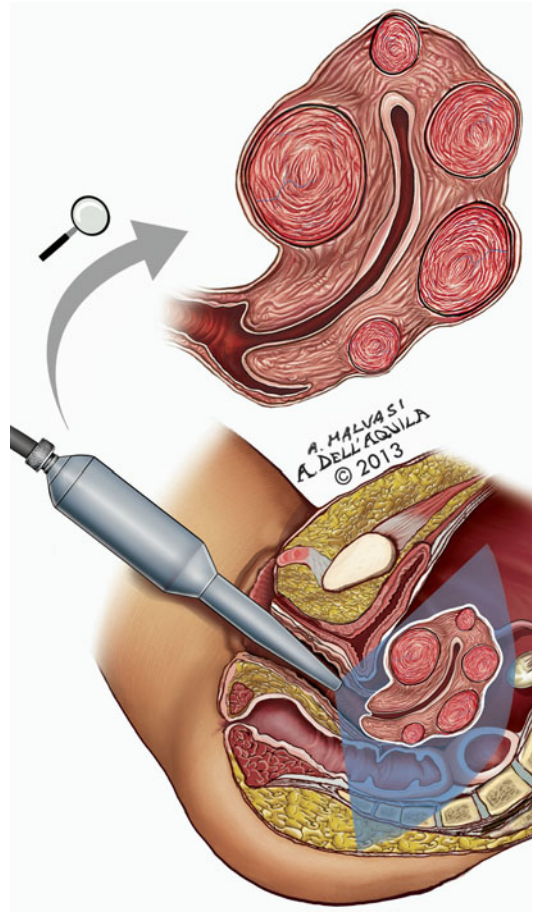

Fig. 4.12 A transvaginal ultrasonography showing a myomatosic uterus

and magnetic resonance imaging (MRI) can all be used to diagnose fibroids. An excellent study used all of these modalities on 106 women and the findings were compared to pathologic assessment following hysterectomy [46].

Submucous fibroids were best identified with MRI (100 % sensitivity, 91 % specificity); next best was saline-infusion sonography (sensitivity, 90 % specificity, 89 %) followed by transvaginal sonography (sensitivity, 83 %, specificity, 90 %) and hysteroscopy (sensitivity, 82 % specificity, 87 %). Sonography is the most readily available and least costly imaging technique to differentiate fibroids from other pelvic pathology and is reasonably reliable for evaluation of uterine volume <375 cc. and containing four or fewer fibroids [47].

MRI is not operator-dependent and has low inter-observer variability for diagnosis of submucous fibroids, intramural fibroids and adenomyosis when compared with TVS, SIS and hysteroscopy [47, 48].

MRI allows evaluation of the number, sizes and positions of submucous, intramural and subserosal fibroids and can evaluate their proximity to the bladder, rectum and endometrial cavity. MRI helps define what can be expected at surgery, and might help the surgeon avoid missing fibroids during surgery [49].

The preoperative diagnosis of leiomyosarcoma using dynamic (timed) MRI with gadolinium may be possible. Diagnosis with total serum LDH, LDH isoenzyme 3 and gadolinium-enhanced dynamic MRI (Gd-DTPA) has been reported to be highly accurate [50].

T1 images should be taken during the arterial phase, between 40 and 60 s after infusion of Gd. Since sarcomas have increased vascularity, they are expected to show increased enhancement with Gadolinium while degenerating fibroids have decreased perfusion and decreased enhancement. Using this protocol in 87 women with fibroids, 10 with leiomyosarcomas and 130 with degenerating fibroids, the authors reported 100 % specificity, 100 % positive predictive value, 100 % negative predictive value and 100 % diagnostic accuracy for leiomyosarcoma. Further investigation of this protocol should be performed to confirm this accuracy.

Treating Pre-operative Anemia

In women with significant pre-operative anemia, intravenous iron can be used to increase hemoglobin levels. A randomized study of women with heavy menstrual bleeding and Hb levels <9.0 g/dl who were scheduled to have surgery received either intravenously iron or oral iron and the mean increase in hemoglobin was higher in the intravenous iron group (3.0 vs. 0.8 g/dl). There were no severe adverse events in either group [51].

Epoetin, a recombinant form of erythropoietin, 250 IU/kg (approximately 15,000 U) per week for 3 weeks prior to elective surgery increased hemoglobin concentrations by 1.6 g/dl and reduce transfusion rates when compared to controls [52].

Also, a study of women with fibroids and mean hemoglobin concentrations of 10.2 g found that after 12 weeks, 74 % of the women treated with GnRH-a and iron had hemoglobins greater than 12 g. compared with 46 % of the women treated with iron alone [53].

New Appearance of Fibroids

Fibroids do not recur; once a fibroid is removed it does not grow back. While new fibroids may arise over time (new appearance), most women will not require additional treatment. If a myomectomy is performed in the presence of a single fibroid (Fig. 4.13), only 11 % of women will need subsequent surgery [54].

If three or more fibroids are removed, only 26 % will need subsequent surgery (mean follow-up 7.6 years). Incomplete follow-up, insufficient length of follow-up, the use of either transabdominal or transvaginal sonography (with different sensitivity), detection of very small, clinically insignificant fibroids, or use of calculations other than life-table analysis confound many studies of new fibroid appearance [38].

Patient symptom questionnaires have a reasonably good correlation with sonographic or pathologic confirmation of significant fibroids and may be the most appropriate method of gauging clinical evidence of new fibroids [7].

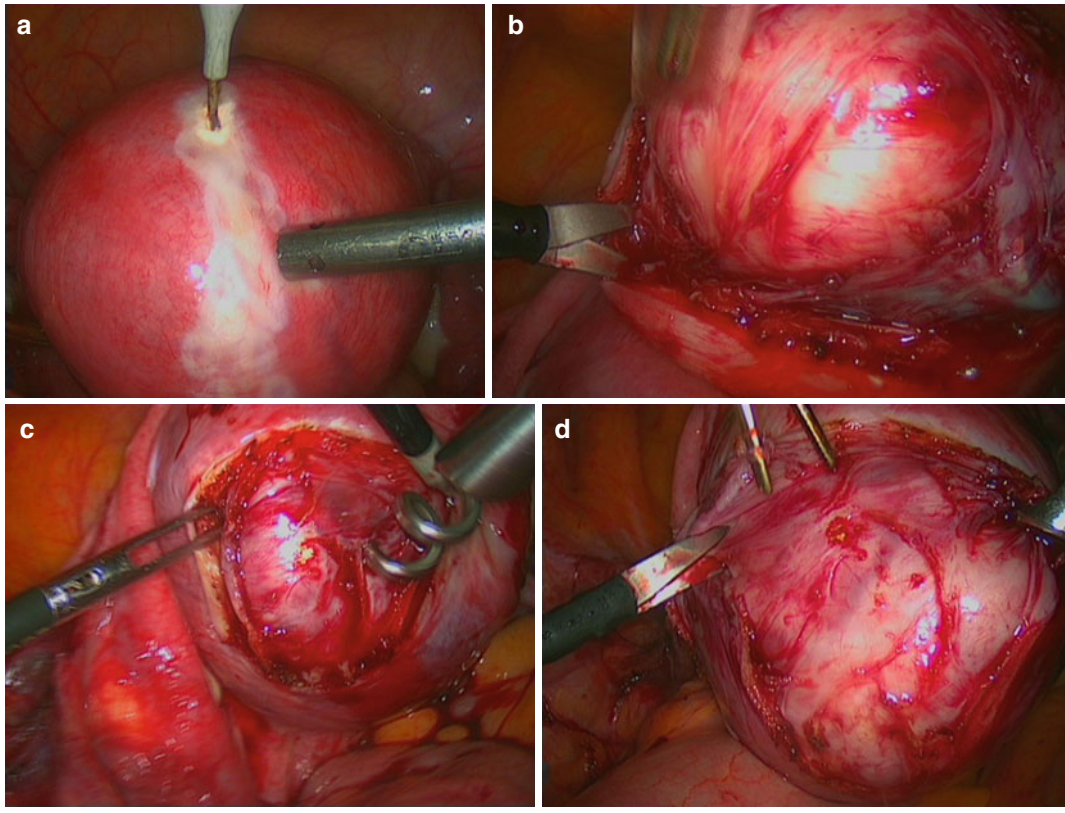

Fig. 4.13 A laparoscopic single myomectomy: (**a**) incision of uterine serosa till the uterine fibroid; (**b**) enucleation of fibroid from its pseudocapsule; (**c**) fibroid traction by a surgical drill; (**d**) fibroid enucleation from uterus

One study of 622 patients followed over 14 years, found new appearance of fibroids discovered with clinical examination and confirmed by ultrasound was 27 % [55]. Ultrasound is sensitive, but detects clinically insignificant fibroids (Fig. 4.14).

Women followed after abdominal myomectomy using clinical evaluation every year and transvaginal sonography at 2 and 5 years found the probability of new appearance by 5 years was 51 % [56]. However, no lower size limit was used for the sonographic diagnosis of fibroids, and this study found many clinically insignificant fibroids. Only 15 % of women with a normal sonogram following an abdominal myomectomy had new fibroids larger than 2 cm, detected over 3 years [57].

Given that the incidence of fibroids increases with increasing age, new fibroids would be expected to form as age increases following myomectomy. Childbearing decreases the risk of new appearance; over 10 years, 16 % for women who subsequently gave birth, and 28 % for those women who did not [55].

Preoperative treatment with GnRH-a decreases fibroid volume and may make smaller fibroids harder to identify during surgery. Three months following abdominal myomectomy, 63 % of women given GnRH had fibroids less than 1.5 cm. detected sonographically, while only 13 % of untreated women had small fibroids detected [56].

New appearance of fibroids is not more common following laparoscopic myomectomy (Fig. 4.15) when compared with abdominal myomectomy. Women randomized to either laparoscopic or abdominal myomectomy were followed with trans-vaginal sonography for 40 months [58].

Fibroids larger than 1 cm, were found in 27 % of women following laparoscopic myomectomy

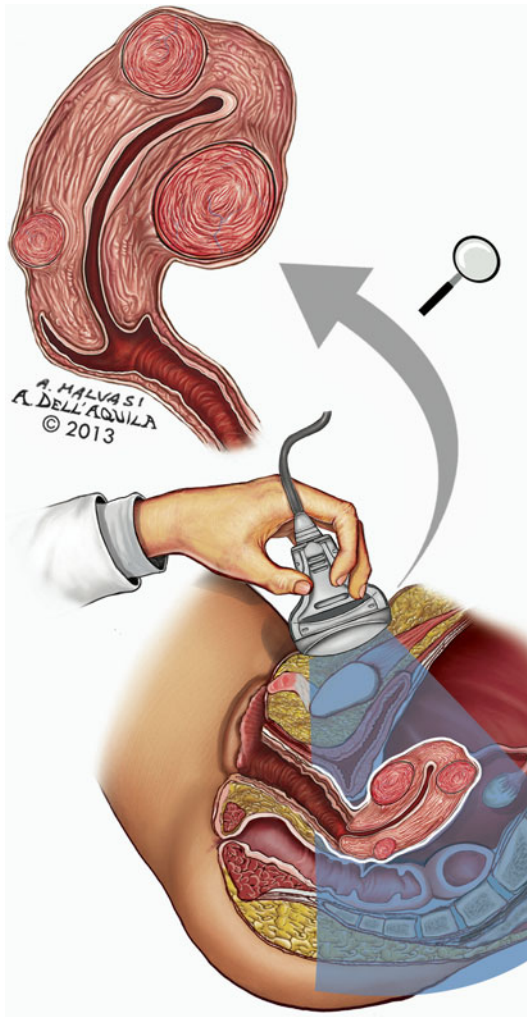

Fig. 4.14 Ultrasound examination is a sensitive instrumental method of fibroids' diagnosis, but often occasionally detects clinically insignificant fibroids

compared with 23 % in the abdominal myomectomy group. No woman in either group required further intervention.

Uterine Changes Following Myomectomy

The uterus heals remarkably well following myomectomy. Using MRI with gadolinium, a Japanese study measured the volume of the uterus 3, 6 and 12 months after myomectomy [59]. Three months following surgery the uterine volume was 75 ml, essentially normal uterine size. Additionally, the authors showed that all women had healing of the endometrium by 12 weeks and that 12 of the 14 women (86 %) had normal blood flow to the myometrium by 12 weeks. Based on this study, it appears that women can start trying to conceive 3 months after myomectomy. Descriptions of surgical technique for abdominal myomectomy usually recommends a multi-layer uterine closure, two layers for myometrium and one for serosa, in order to achieve hemostasis and avoid hematoma formation [60, 61].

Electro-surgery is rarely used for hemostasis. Variations of this technique have been described, and all appear to be associated with low rates of uterine rupture [62, 63]. A retrospective study of 412 women who had abdominal myomectomies reported only one woman with uterine rupture (0.2 %) [64].

The Risk of Uterine Rupture After Myomectomy

The risk of uterine rupture following laparoscopic myomectomy has not been well studied. However, a review of 19 cases of uterine rupture during pregnancy revealed deviation from established technique that might interfere with wound healing in 18 cases: only three cases had multi-layered closures of the uterine defects; electrosurgery was used for hemostasis (rather than suturing) in 17 cases; and for only one case was no ostensible factor found for uterine rupture [65].

Uterine scars resulting from abdominal (n = 10) or laparoscopic (n = 5) myomectomy have been examined at the time of subsequent cesarean section [66].

Following abdominal myomectomies, the scars were of similar thickness to normal myometrium. In contrast, the scars following laparoscopic myomectomy were very strained, had poorly defined edges, and were more contracted and thinner than normal myometrium. The authors concluded that these differences were likely due to the use of sutures to achieve

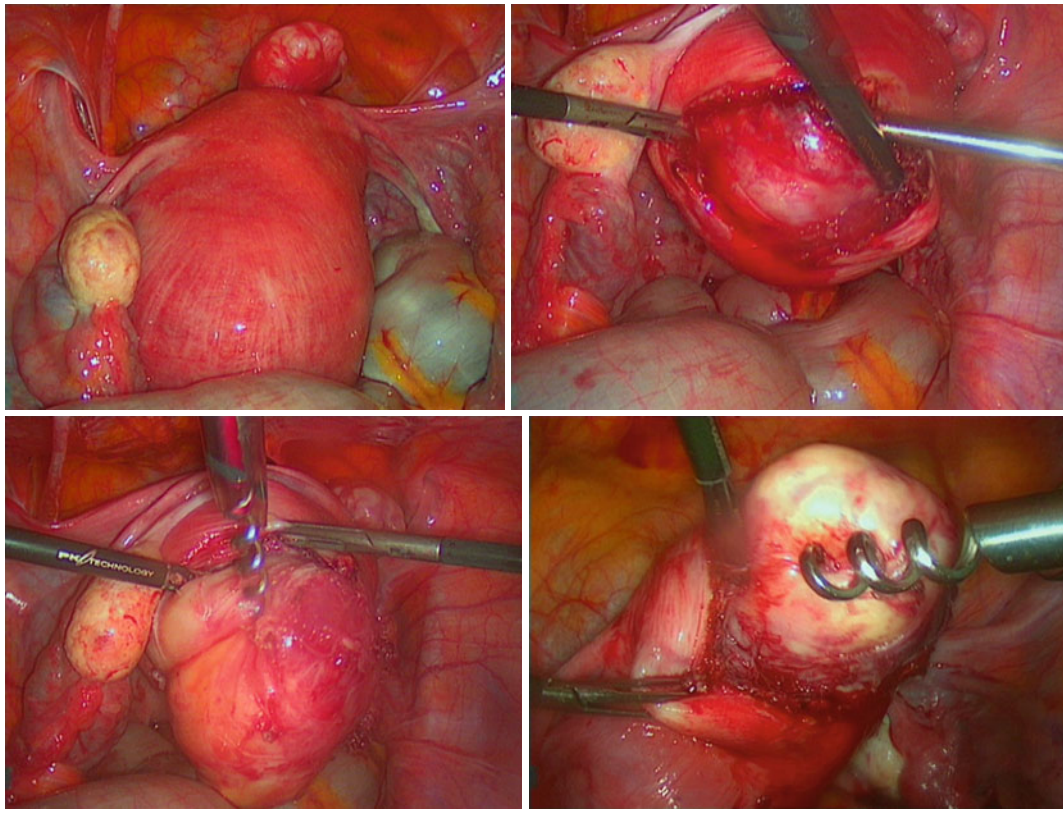

Fig. 4.15 A sequence of laparoscopic myomectomy; in clockwise fashion from the *left top* to the *lower left*, a uterus with a large posterior fibroid, with uterine serosa incision and fibroid enucleation with the progressive traction by drill

hemostasis during abdominal myomectomy, whereas bipolar coagulation was used during laparoscopic myomectomy. Resultant thermal damage to the myometrium induces proliferation of connective tissue, which cannot remodel during pregnancy.

Tissue sampling of uterine dehiscence shows high collagen content and reduction of smooth muscle fibers, which likely accounts for decreased tensile strength of the myometrium [67].

Tissue sampling of the scar shows a marked decrease of transforming growth factor–b3 (TGF-B), a reduction of connective tissue growth factor (CTGF), an increase in basic fibroblast growth factor (bFGF) and slight enhancement in vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and tumor necrosis factor alpha (TNF-A) expression, all known to be important for wound healing.

Ultrasonographic evaluation of abdominal myomectomy scars performed 60–90 days following surgery found mixed echogenic areas, thought to represent the result of hyperplastic myometrium, small hematomas and suture material. Gradual shrinkage of the myometrium, resolution of hematomas and absorption of suture material led to a decrease in the size of the scar over 3 months [68].

Using sonographic evaluation, a preoperative myoma size greater than 10 cm and the experience of the surgeon were significantly correlated with formation of uterine scar hematomas. Wound healing appeared complete within 3 months [69]. A study of laparoscopic myomectomy scars found in 8 % of women 6 weeks following surgery [70].

The authors suggested hematomas resulted from closure of the uterine defect with only a single layer of sutures. Nevertheless, imaging

studies examine surrogate outcomes of wound healing, but not wound strength. Presently, it appears prudent for surgeons to adhere to time-tested techniques developed for abdominal myomectomy, including limited use of electro-surgery and multi-layered closure of myometrium in other than superficial uterine defects. Yet, even with ideal surgical technique, individual wound healing characteristics may predispose to uterine rupture.

References

1. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol. 2012;206:211.e1–9.
2. Fernandez H, Farrugia M, Jones SE, Mauskopf JA, Oppelt P, Subramanian D. Rate, type, and cost of invasive interventions for uterine myomas in Germany, France, and England. J Minim Invasive Gynecol. 2009;16:40–6.
3. Whiteman MK, Hillis SD, Jamieson DJ, et al. Inpatient hysterectomy surveillance in the United States, 2000–2004. Am J Obstet Gynecol. 2008;198:34.e1–7.
4. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol. 1990;94:435–8.
5. Day Baird D, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol. 2003;188:100–7.
6. Peddada SD, Laughlin SK, Miner K, Guyon JP, Haneke K, Vahdat HL, Semelka RC, Kowalik A, Armao D, Davis B, Baird DD. Growth of uterine leiomyomata among premenopausal black and white women. Proc Natl Acad Sci U S A. 2008;105(50):19887–92.
7. Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol. 1997;90:967–73.
8. Kjerulff KH, Langenberg P, Seidman JD, Stolley PD, Guzinski GM. Uterine leiomyomas. Racial differences in severity, symptoms and age at diagnosis. J Reprod Med. 1996;41:483–90.
9. Vikhlyaeva EM, Khodzhaeva ZS, Fantschenko ND. Familial predisposition to uterine leiomyomas. Int J Gynaecol Obstet. 1995;51:127–31.
10. Marshall LM, Spiegelman D, Goldman MB, Manson JE, Colditz GA, Barbieri RL, et al. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril. 1998;70:432–9.
11. Cramer SF, Marchetti C, Freedman J, Padela A. Relationship of myoma cell size and menopausal status in small uterine leiomyomas. Arch Pathol Lab Med. 2000;124:1448–53.
12. Cook JD, Walker CL. Treatment strategies for uterine leiomyoma: the role of hormonal modulation. Semin Reprod Med. 2004;22:105–11.
13. Englund K, Blanck A, Gustavsson I, Lundkvist U, Sjoblom P, Norgren A, et al. Sex steroid receptors in human myometrium and fibroids: changes during the menstrual cycle and gonadotropin-releasing hormone treatment. J Clin Endocrinol Metab. 1998;83:4092–6.
14. Nisolle M, Gillerot S, Casanas-Roux F, Squifflet J, Berliere M, Donnez J. Immunohistochemical study of the proliferation index, oestrogen receptors and progesterone receptors A and B in leiomyomata and normal myometrium during the menstrual cycle and under gonadotrophin-releasing hormone agonist therapy. Hum Reprod. 1999;14:2844–50.
15. Kawaguchi K, Fujii S, Konishi I, Nanbu Y, Nonogaki H, Mori T. Mitotic activity in uterine leiomyomas during the menstrual cycle. Am J Obstet Gynecol. 1989;160:637–41.
16. Orsini G, Laricchia L, Fanelli M. Low-dose combination oral contraceptives use in women with uterine leiomyomas. Minerva Ginecol. 2002;54:253–61.
17. Parazzini F, Negri E, La Vecchia C, Fedele L, Rabaiotti M, Luchini L. Oral contraceptive use and risk of uterine fibroids. Obstet Gynecol. 1992;79:430–3.
18. Samadi AR, Lee NC, Flanders WD, Boring 3rd JR, Parris EB. Risk factors for self-reported uterine fibroids: a case-control study. Am J Public Health. 1996;86:858–62.
19. Ross RK, Pike MC, Vessey MP, Bull D, Yeates D, Casagrande JT. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. Br Med J (Clin Res Ed). 1986;293:359–62.
20. Ratner H. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. Br Med J (Clin Res Ed). 1986;293:1027.
21. Palomba S, Sena T, Morelli M, Noia R, Zullo F, Mastrantonio P. Effect of different doses of progestin on uterine leiomyomas in postmenopausal women. Eur J Obstet Gynecol Reprod Biol. 2002;102:199–201.
22. Reed SD, Cushing-Haugen KL, Daling JR, Scholes D, Schwartz SM. Postmenopausal estrogen and progestogen therapy and the risk of uterine leiomyomas. Menopause. 2004;11:214–22.
23. Parazzini F, Negri E, La Vecchia C, Chatenoud L, Ricci E, Guarnerio P. Reproductive factors and risk of uterine fibroids. Epidemiology. 1996;7:440–2.
24. Lumbiganon P, Rugpao S, Phandhu-fung S, Laopaiboon M, Vudhikamraksa N, Werawatakul Y. Protective effect of depot-medroxyprogesterone acetate on surgically treated uterine leiomyomas: a multicentre case-control study. Br J Obstet Gynaecol. 1996;103:909–14.
25. Baird DD, Dunson DB. Why is parity protective for uterine fibroids? Epidemiology. 2003;14:247–50.

26. Cesen-Cummings K, Houston KD, Copland JA, Moorman VJ, Walker CL, Davis BJ. Uterine leiomyomas express myometrial contractile-associated proteins involved in pregnancy-related hormone signaling. J Soc Gynecol Investig. 2003;10:11–20.
27. Burbank F. Childbirth and myoma treatment by uterine artery occlusion: do they share a common biology? J Am Assoc Gynecol Laparosc. 2004;11: 138–52.
28. Chiaffarino F, Parazzini F, La Vecchia C, Chatenoud L, Di Cintio E, Marsico S. Diet and uterine myomas. Obstet Gynecol. 1999;94:395–8.
29. Baird D, Dunson D, Hill M, Cousins D, Schectman J. Association of physical activity with development of uterine leiomyoma. Am J Epidemiol. 2007;165: 157–63.
30. Barbieri RL, McShane PM, Ryan KJ. Constituents of cigarette smoke inhibit human granulosa cell aromatase. Fertil Steril. 1986;46:232–6.
31. Daniel M, Martin AD, Drinkwater DT. Cigarette smoking, steroid hormones, and bone mineral density in young women. Calcif Tissue Int. 1992;50:300–5.
32. Rowe MK, Kanouse DE, Mittman BS, Bernstein SJ. Quality of life among women undergoing hysterectomies. Obstet Gynecol. 1999;93:915–21.
33. Munro MG, Lukes AS. Abnormal uterine bleeding and underlying hemostatic disorders: report of a consensus process. Fertil Steril. 2005;84:1335–7.
34. Wegienka G, Baird DD, Hertz-Picciotto I, Harlow SD, Steege JF, Hill MC, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol. 2003;101:431–7.
35. Moshesh M, Olshan AF, Saldana T, Baird D. Examining the relationship between uterine fibroids and dyspareunia among premenopausal women in the United States. J Sex Med. 2014;11:800–8.
36. Murase E, Siegelman ES, Outwater EK, Perez-Jaffe LA, Tureck RW. Uterine leiomyomas: histopathologic features, MR imaging findings, differential diagnosis, and treatment. Radiographics. 1999;19(5):1179–97.
37. Gaym A, Tilahun S. Torsion of pedunculated subserous myoma–a rare cause of acute abdomen. Ethiop Med J. 2007;45(2):203–7.
38. Olive DL. Review of the evidence for treatment of leiomyomata. Environ Health Perspect. 2000;108 Suppl 5:841–3.
39. Langer R, Golan A, Neuman M, Schneider D, Bukovsky I, Caspi E. The effect of large uterine fibroids on urinary bladder function and symptoms. Am J Obstet Gynecol. 1990;163:1139–41.
40. Parker W, Fu Y, Berek J. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol. 1994;83: 414–8.
41. Boutselis J, Ullery J. Sarcoma of the uterus. Obstet Gynecol. 1962;20:23–35.
42. Brooks SE, Zhan M, Cote T, Baquet CR. Surveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989–1999. Gynecol Oncol. 2004;93:204–8.
43. Quade BJ, Wang TY, Sornberger K, Dal Cin P, Mutter GL, Morton CC. Molecular pathogenesis of uterine smooth muscle tumors from transcriptional profiling. Genes Chromosomes Cancer. 2004;40:97–108.
44. Carlson KJ, Miller BA, Fowler Jr FJ. The Maine Women's Health Study: II. Outcomes of nonsurgical management of leiomyomas, abnormal bleeding, and chronic pelvic pain. Obstet Gynecol. 1994;83:566–72.
45. Cantuaria GH, Angioli R, Frost L, Duncan R, Penalver MA. Comparison of bimanual examination with ultrasound examination before hysterectomy for uterine leiomyoma. Obstet Gynecol. 1998;92:109–12.
46. Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Evaluation of the uterine cavity with magnetic resonance imaging, transvaginal sonography, hysterosonographic examination, and diagnostic hysteroscopy. Fertil Steril. 2001;76:350–7.
47. Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. Am J Obstet Gynecol. 2002;186:409–15.
48. Dueholm M, Lundorf E, Sorensen JS, Ledertoug S, Olesen F, Laursen H. Reproducibility of evaluation of the uterus by transvaginal sonography, hysterosonographic examination, hysteroscopy and magnetic resonance imaging. Hum Reprod. 2002;17:195–200.
49. Dueholm M, Lundorf E, Olesen F. Imaging techniques for evaluation of the uterine cavity and endometrium in premenopausal patients before minimally invasive surgery. Obstet Gynecol Surv. 2002;57: 388–403.
50. Goto A, Takeuchi S, Sugimura K, Maruo T. Usefulness of Gd-DTPA contrast-enhanced dynamic MRI and serum determination of LDH and its isozymes in the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus. Int J Gynecol Cancer. 2002;12:354–61.
51. Kim YH, Chung HH, Kang SB, Kim SC, Kim YT. Safety and usefulness of intravenous iron sucrose in the management of preoperative anemia in patients with menorrhagia: a phase IV, open-label, prospective, randomized study. Acta Haematol. 2009;121: 37–41.
52. Wurnig C, Schatz K, Noske H, Hemon Y, Dahlberg G, Josefsson G, et al. Subcutaneous low-dose epoetin beta for the avoidance of transfusion in patients scheduled for elective surgery not eligible for autologous blood donation. Eur Surg Res. 2001;33:303–10.
53. Stovall TG, Muneyyirci-Delale O, Summitt Jr RL, Scialli AR. GnRH agonist and iron versus placebo and iron in the anemic patient before surgery for leiomyomas: a randomized controlled trial. Leuprolide Acetate Study Group. Obstet Gynecol. 1995;86:65–71.
54. Malone L. Myomectomy: recurrence after removal of solitary and multiple myomas. Obstet Gynecol. 1969;34:200–3.
55. Candiani GB, Fedele L, Parazzini F, Villa L. Risk of recurrence after myomectomy. Br J Obstet Gynaecol. 1991;98:385–9.

56. Fedele L, Parazzini F, Luchini L, Mezzopane R, Tozzi L, Villa L. Recurrence of fibroids after myomectomy: a transvaginal ultrasonographic study. Hum Reprod. 1995;10:1795–6.
57. Vavala V, Lanzone A, Monaco A, Scribanti A, Guida C, Mancuso S. Postoperative GnRH analog treatment for the prevention of recurrences of uterine myomas after myomectomy. A pilot study. Gynecol Obstet Invest. 1997;43:251–4.
58. Rossetti A, Sizzi O, Soranna L, Cucinelli F, Mancuso S, Lanzone A. Long-term results of laparoscopic myomectomy: recurrence rate in comparison with abdominal myomectomy. Hum Reprod. 2001;16:770–4.
59. Tsuji S, Takahashi K, Imaoka I, Sugimura K, Miyazaki K, Noda Y. MRI evaluation of the uterine structure after myomectomy. Gynecol Obstet Invest. 2006;61:106–10.
60. Guarnaccia MM, Rein MS. Traditional surgical approaches to uterine fibroids: abdominal myomectomy and hysterectomy. Clin Obstet Gynecol. 2001;44(2):385–400.
61. West S, Ruiz R, Parker W. Abdominal myomectomy in women with very large uterine size. Fertil Steril. 2006;85:36–9.
62. Garnet JD. Uterine rupture during pregnancy. an analysis of 133 patients. Obstet Gynecol. 1964;23:898–905.
63. Palerme GR, Friedman EA. Rupture of the gravid uterus in the third trimester. Am J Obstet Gynecol. 1966;94:571–6.
64. Obed J, Omigbodun A. Rupture of the uterus in patients with previous myomectomy and primary caesarean section scars: a comparison. J Obstet Gynaecol. 1996;1:1621.
65. Parker WH, Einarsson J, Istre O, Dubuisson JB. Risk factors for uterine rupture after laparoscopic myomectomy. J Minim Invasive Gynecol. 2010;17:551–4.
66. Cobellis L, Pecori E, Cobellis G. Comparison of intramural myomectomy scar after laparotomy or laparoscopy. Int J Gynaecol Obstet. 2004;84:87–8.
67. Pollio F, Staibano S, Mascolo M, Salvatore G, Persico F, De Falco M, Di Lieto A. Uterine dehiscence in term pregnant patients with one previous cesarean delivery: growth factor immunoexpression and collagen content in the scarred lower uterine segment. Am J Obstet Gynecol. 2006;194:527–34.
68. Tepper R, Beyth Y, Klein Z, Aviram R. Postmyomectomy sonographic imaging: uterus remodeling and scar repair. Arch Gynecol Obstet. 2009;280:509–11.
69. Darwish AM, Nasr AM, El-Nashar DA. Evaluation of postmyomectomy uterine scar. J Clin Ultrasound. 2005;33:181–6.
70. Keckstein J, Karageorgieva E, Darwish A, et al. Laparoscopic myomectomy sonographic follow-up and second-look laparoscopy for the evaluation of a new technique. J Am Assoc Gynecol Laparosc. 1994;4(pt 2):S16.

Uterine Myomas and Fertility

5

Liselotte Mettler, Anupama Deenadayal, and Ibrahim Alkatout

Introduction

Within the field of human reproduction this benign disease raises many questions.

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

L. Mettler (✉) • A. Deenadayal • I. Alkatout
Department Obstetrics and Gynecology,
University Clinics Schleswig-Holstein,
Campus Kiel, Arnold-Heller-Str. 3, House 24,
Kiel 24105, Germany
e-mail: lmettler@email.uni-kiel.de;
ibrahim.alkatout@gmail.com

Etiology, Pathophysiology and Genetic Origin

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 funtionalis (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

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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 myome trial 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 Progestrone 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 (tenesms). 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 speak 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 versus 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, 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 glycodelin 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 DR (Delivery Rate) 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 masseffect 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 cut-off 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 (acreta, increta, percreta, praevia) and a risk of uterine rupture. In our different evaluations of abdominal and laparoscopic myomectomies in more than 2,000 cases over 20 years as well as over 500 hysteroscopic myomectomies, only one uterine rupture occured 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 versus 22 %) and Caesarean sections (65 versus 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 Caesarean sections [30]. Dubuisson describes three uterine ruptures, all occurring before labour 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 Caesarean 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. 5.1. 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 who had undergone LM (Laparoscopic Myomectomy) 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 MRI guided Ultrasound (MgRfoUS) 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.

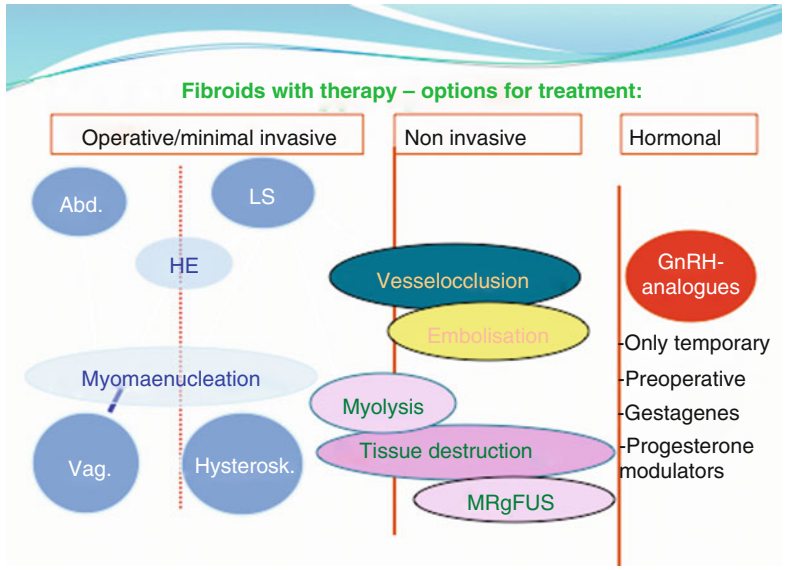

Fig. 5.1 Treatment options for uterine fibroids

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 whilst respecting the pseudocapsule by neurofibre 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 intra-cavity extension of the fibroid can be noted. A chrompertubation 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 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, and 5.8 give a detailed diagnostic and surgical description of myomectomy and surgical reconstruction of the uterine wall.

This step wise 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 one, two or three 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.

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].

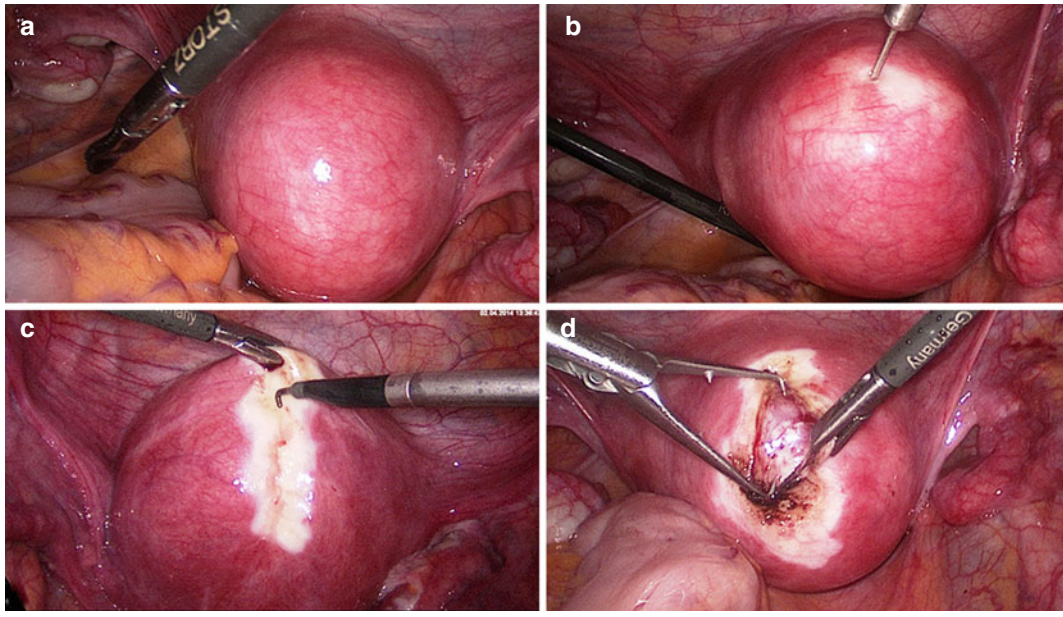

Fig. 5.2 Laparoscopic myoma enucleation. (**a**) Situs of a fundal/anterior wall fibroid. (**b**) Prophylactic hemostasis with 1:100 diluted vasopressin solution (Gylcilpressin) in separate wells. The injection intends to separate the pseudocapsule from the fibroid and reduces bleedings. (**c**) Bipolar 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

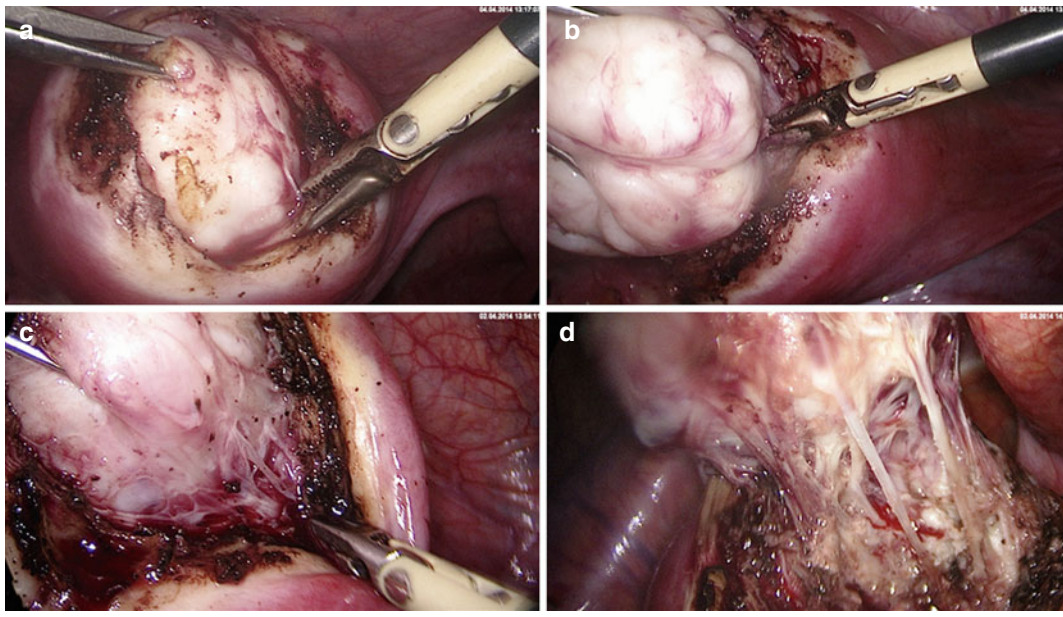

Fig. 5.3 Laparoscopic myoma enucleation. (**a**) Traction of the fibroid with a tenaculum and blunt delineation from the capsule. (**b**) Focal bipolar coagulation of basic vessels. (**c**) Continuous enucleation of the fibroid under traction and specific coagulation of capsule fibers containing vessels. (**d**) Magnification of remaining capsule fibers to be coagulated and cut

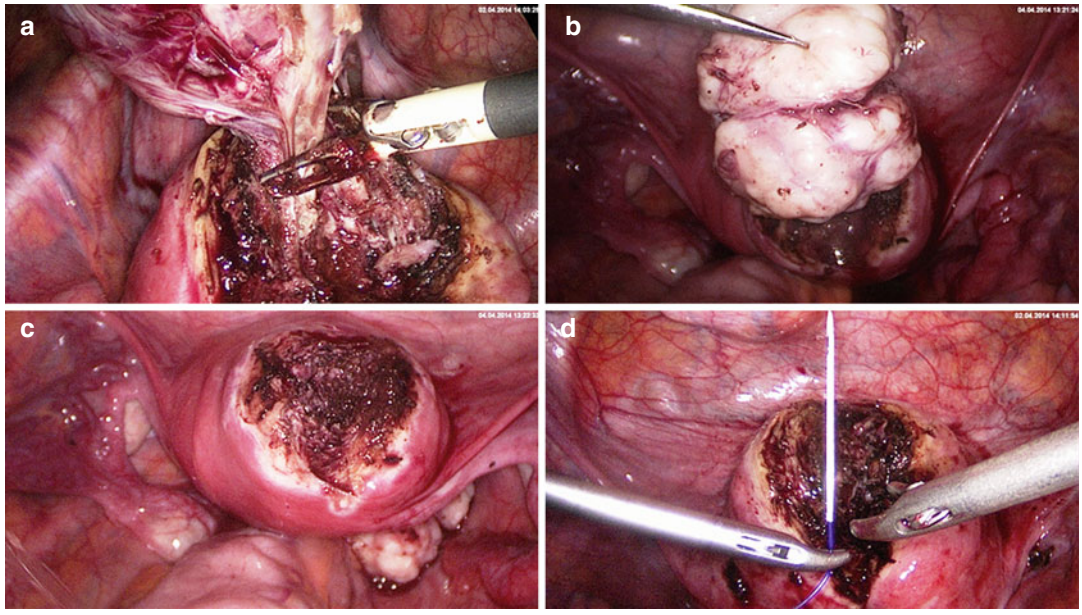

Fig. 5.4 Laparoscopic myoma enucleation. (**a**) Final coagulation of the capsule vessels. (**b**) Double belly fibroid after complete enucleation. (**c**) Minimal coagulation of bleeding vessels under suction and irrigation. (**d**) Approximation of wound edges with either straight or round sharp needle and a monofilar late resorbable suture

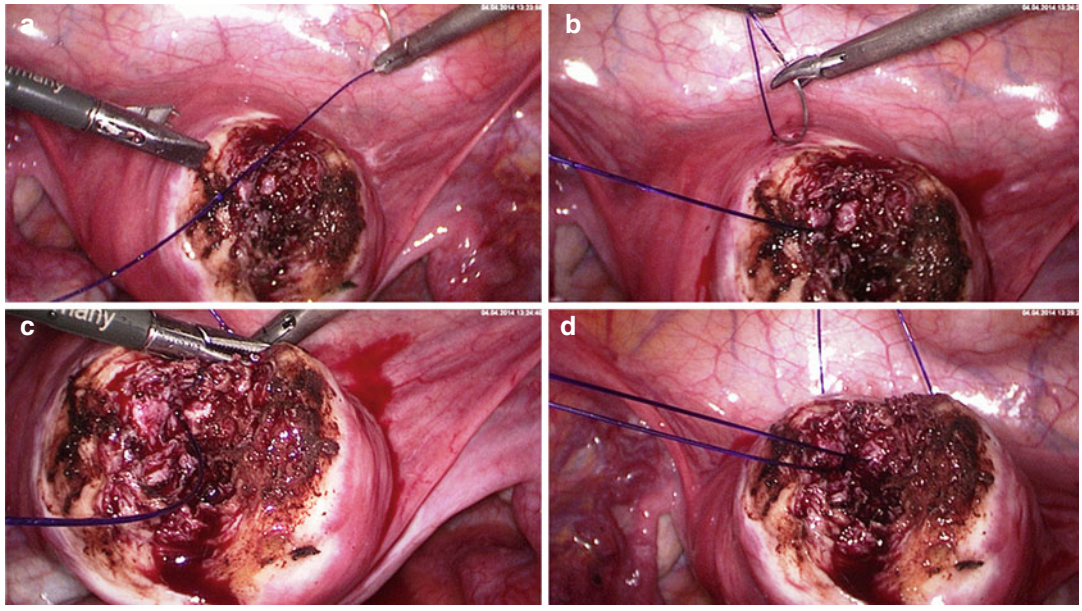

Fig. 5.5 Laparoscopic myoma enucleation. (**a**) Advantage of round needle stich. The wound angle is elevated safely and completely by elevating it with a Manhes-forceps. Deeper layers of the myometrium can be grasped more easily using a round needle. (**b**) Needle exit and simplified regrasping with the right needle holder. (**c**) Final stich to invert the knot. (**d**) Extirpation of the needle and completing the extracorporal knot and preparing to push down the extracorporal knot

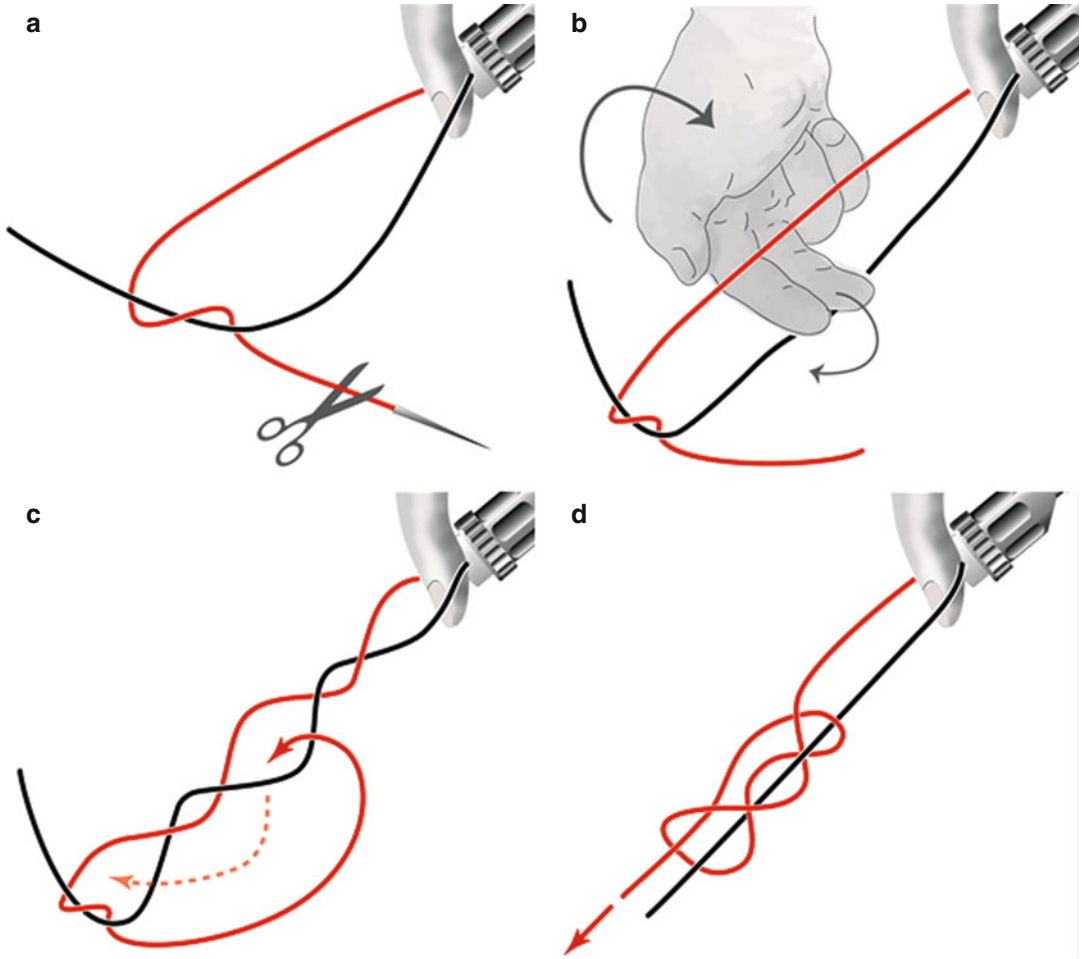

Fig. 5.6 Performance of the extracorporal "von Leffern" knot. (**a**) Pulling out the suture, removing the needle, half hitch. (**b**) Holding the knot with the left hand and reaching over with the right hand. (**c**) Grasping the short end from below and leading it back, exiting before the half hitch. (**d**) Turning back the knot. Holding the straight suture and tightening the knot

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 are of mesothelial origin and affect 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

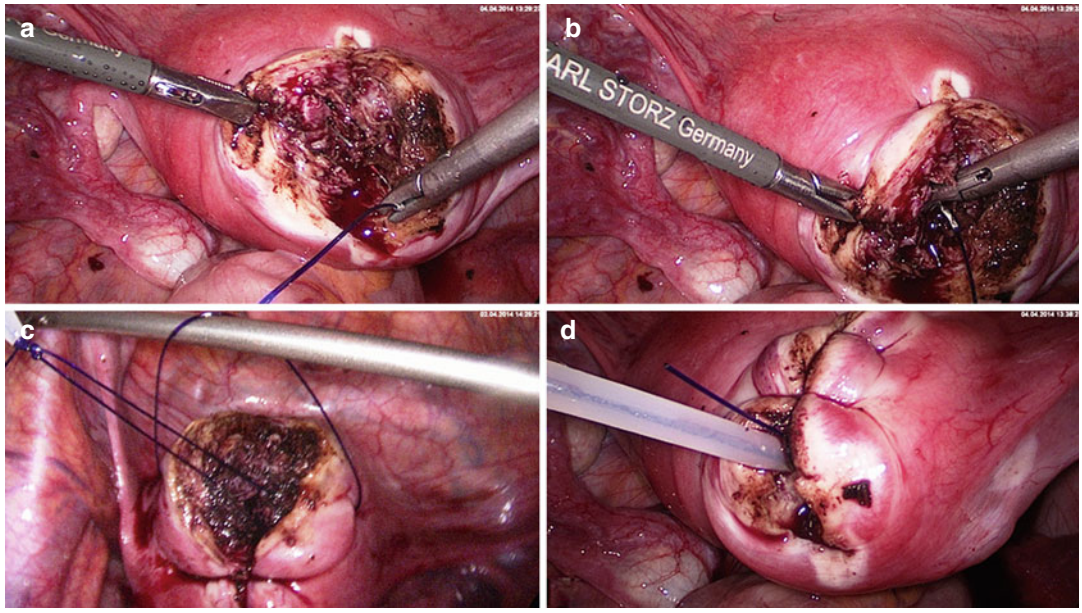

Fig. 5.7 Laparoscopic myoma enucleation. (**a**) Second single stich starting as deep as possible in the uterine wound. (**b**) Exiting of the needle on the left wound margin (just next to the Manhes forceps). (**c**) Completing of the stich and preparation of the extracorporal von Leffern knot. The needle holder elevates the thread to avoid tearing of the uterine wall while pulling through the monofilar thread (PDS). (**d**) Pushing down the extracorporal performed knot with a plastic push-rod in the depth of the wound to dump the knot minimizing the external suture part

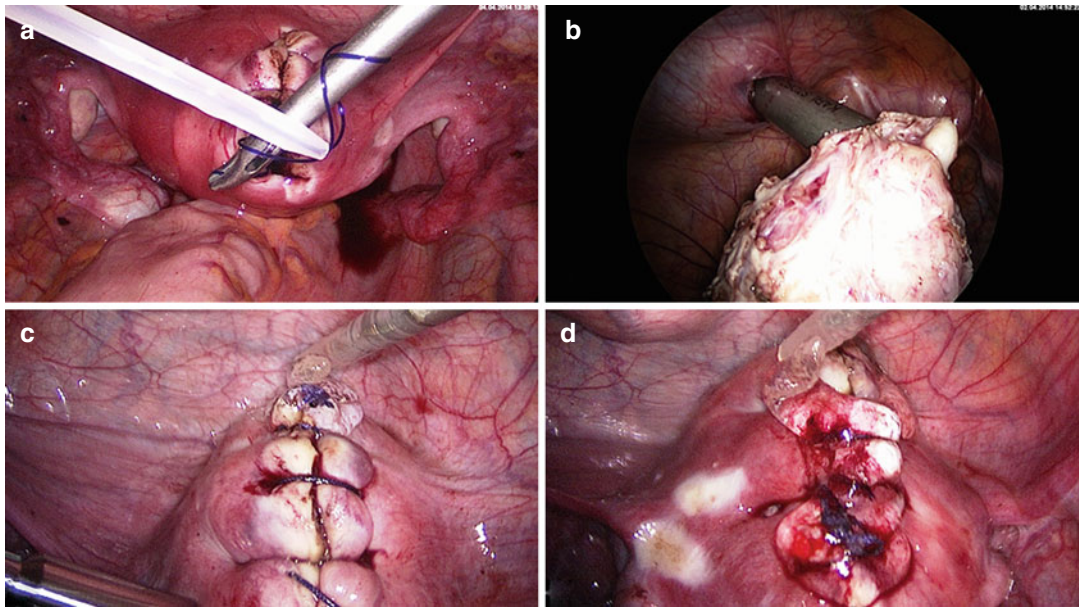

Fig. 5.8 Laparoscopic myoma enucleation. (**a**) Intracorporal safety knot of the performed extracorporal knot. (**b**) Morcellation of the fibroid with the Rotocut morcellator (Storz) in an apple peeling manner. (**c**) Final situs showing the extracorporal sutures to adapt the uterine wound edges. (**d**) Application of Hyalobarrier® (Nordic Pharma) for adhesion prevention

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 2 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 unsuspicious-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. 5.9). 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.

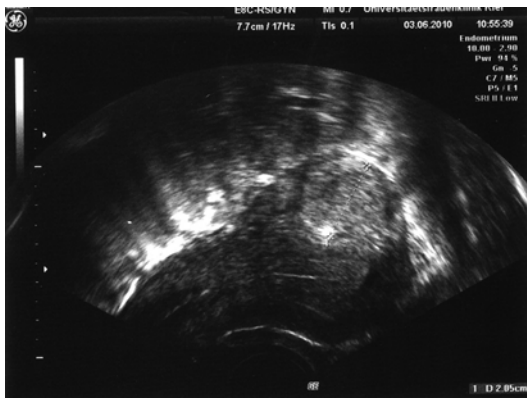

Fig. 5.9 Preoperative transvaginal ultrasound scan showing the typical misleading sonographic picture of a fibroid (case 1)

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. 5.10a). After removal of the nodule and the surrounding myometrial layer, the uterine wall was reconstructed in a single layer with reversed and inverted single stitches (Fig. 5.10b). The tumor was removed after intraabdominal morcellation (Fig. 5.10c).

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

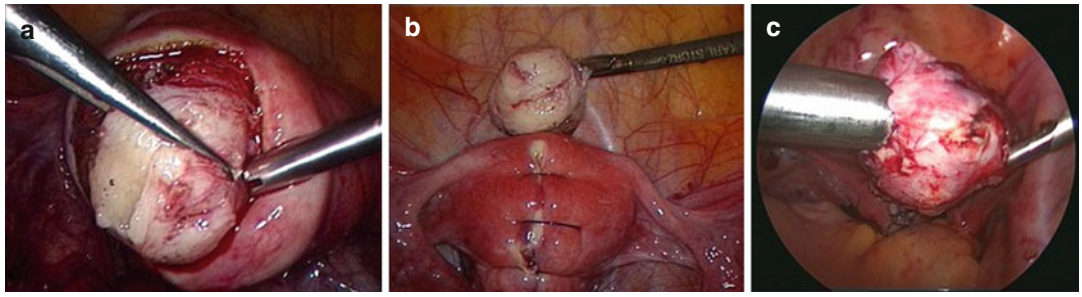

Fig. 5.10 (**a**) Intraoperative sight of the adenomatoid tumor connected to the surrounding myometrium (case 1). (**b**) Reconstruction of the uterine wall after excision of the tumor (case 1). (**c**) Removing the adenomatoid tumor by morcellation (case 2)

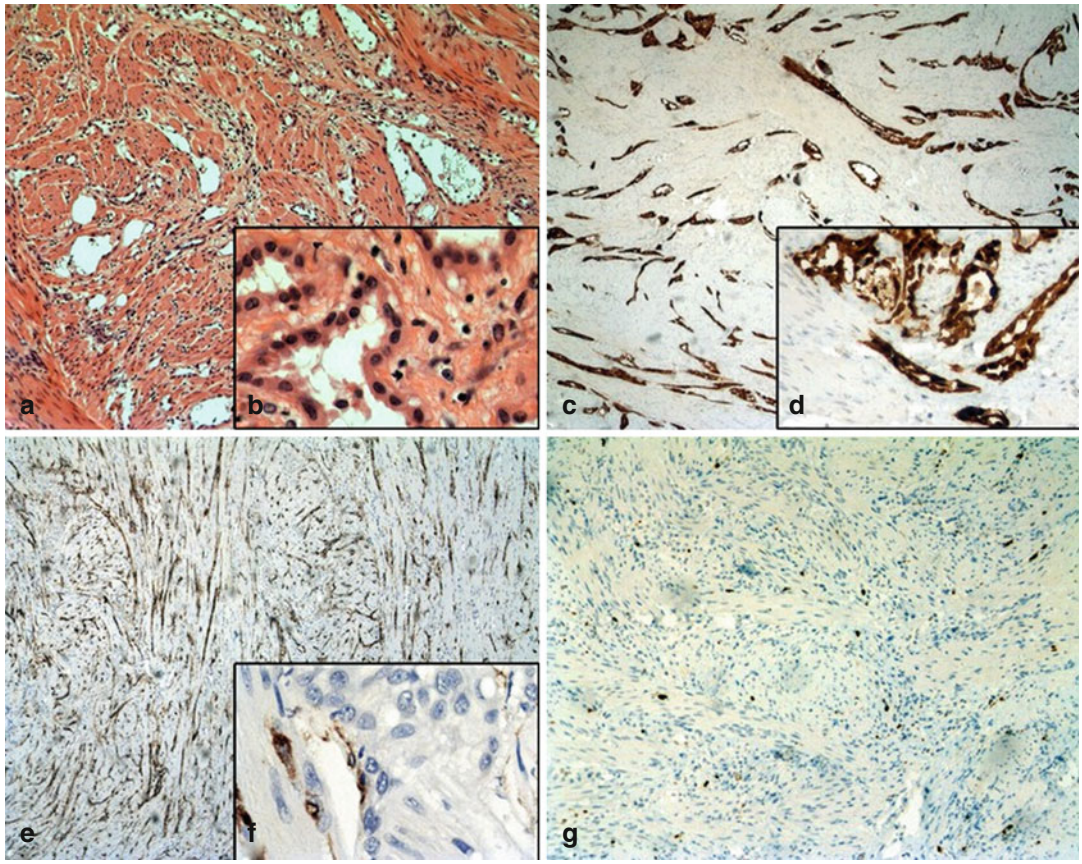

Fig. 5.11 (**H&E**): (**a**) low magnification (×25) of the uterine adenomatoid tumor showing the typical tubular-glandular growth pattern and surrounding small muscle cells. (**b**) The lining cells in typical cuboidal growth pattern with unsuspicious nuclei at high magnification (×400). (**Calretintin**): (**c**) showing the strongly positive immunohistochemical calretinin staining of the tumor tissue (×25×). (**d**) Positive stained tumor cells at high magnification (×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 (×25 and ×400). (**Ki-67**): Immunohistochemical Ki-67 staining (10×) showing no enhanced mitotic activity of the tumor tissue (**g**)

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 tumour and reconstruction of uterus wall.

The post-operative 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-µm 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-grey, 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. 5.11a, 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 or necrosis were found.

Immunohistochemical techniques showed a strong staining of tumor cells with calretinin but no staining with CD34 (Fig. 5.11c, d). However, CD34 marked the endothelial cells and the surrounding orthotopic lymphovascular vessels (Fig. 5.11e, f). The Ki-67 index of the tumor cells was <1 % (Fig. 5.11g).

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 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 epididymidis, tunica albuginea and testicular parenchyma. Very seldom, adenomatoid tumors are seen in extragenital regions e.g. 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, infiltrates 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 mesothelian 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 supports the mesothelian concept. Nevertheless, the pathogenesis remains uncertain, as the superficial location suggests a peritoneal origin whereas the mesothelian 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 Ki67. Other markers are HMBE1, other cytoceratins, 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 non-recurring, 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.

Recurrence Rates

Even with the best, at this moment, surgical intracapsular excision of fibroids gives no guarantee of a non-recurrence 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 pre-operatively. 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 three cases (0.8 %) with endometriosis and in three cases (0.8 %) with ovarian cysts [62].

Location of Myoma

The different locations of myomas are clearly visible in Fig. 5.12. The location of fibroids were 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 and in 8 % intramural. In 33 patients adhesiolysis was necessary prior to the myomectomy.

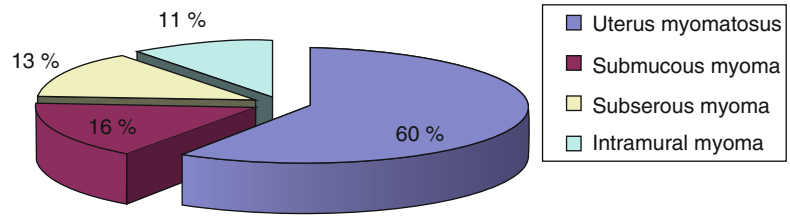

Fig. 5.12 Localization of myomas in the 392 patients

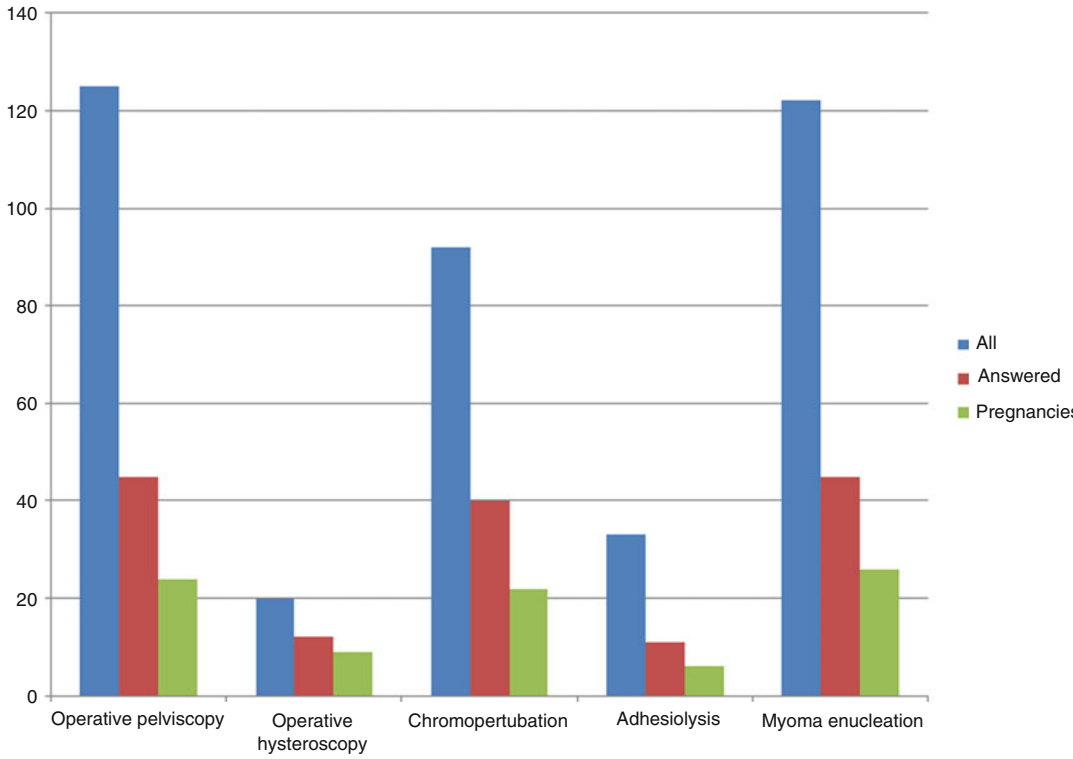

Fig. 5.13 Laparoscopic surgical procedures performed for infertility according to groups A, B and C

Figure 5.13 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. 5.14).

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. 5.15 and 5.16). The lowest pregnancy rate was achieved after intramural fibroid resection.

Mode of Delivery

Eleven of the 129 myomectomy patients underwent a caesarean 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

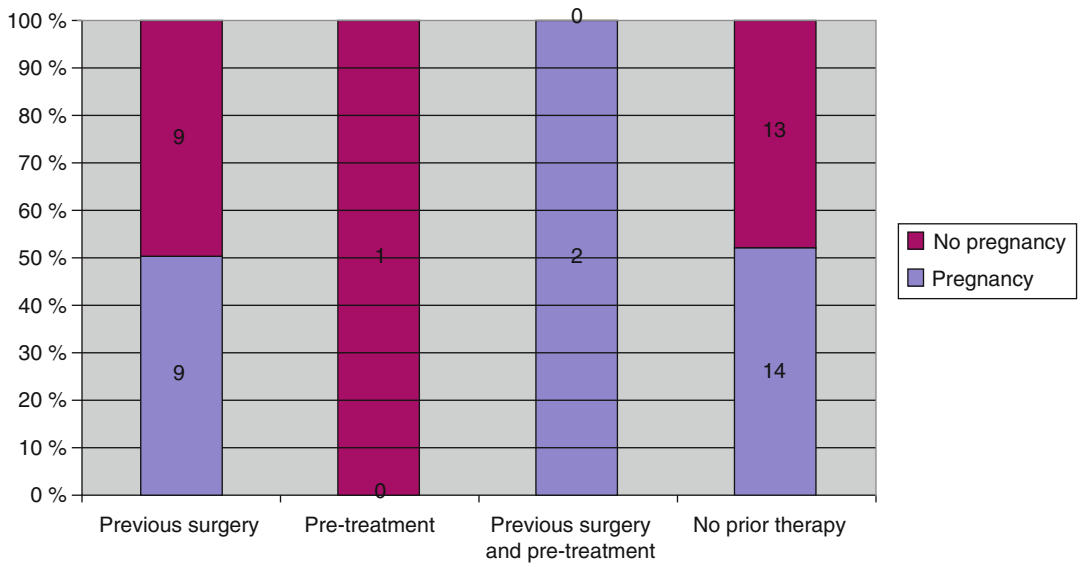

Fig. 5.14 Influence of surgery and pre-treatment on pregnancy rates of patients with myomas

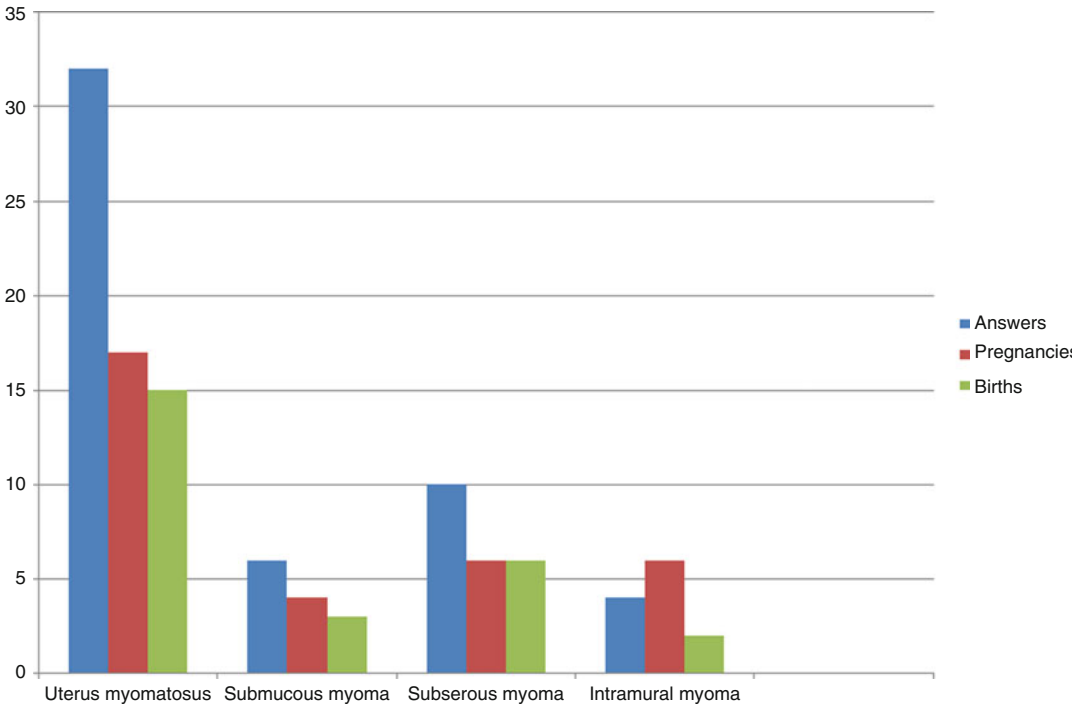

Fig. 5.15 Number of pregnancies and deliveries according to localization of myoma with display of answers

spontaneous and 7 (58 %) caesarean 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

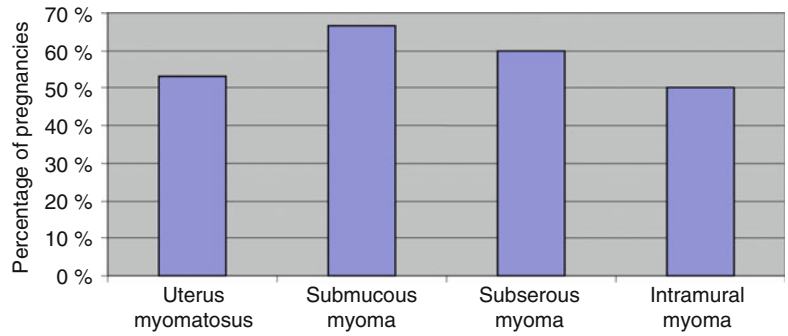

Fig. 5.16 Number of pregnancies according to myoma localization

descent after delivery, placenta accreta, one uterine rupture with caesarean section and one emergency caesarean 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.

Discussion and 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 [63]. Myomectomies at caesarean sections have led to dramatic complications and it is not advisable to be performed at that time [64].

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.

References

1. Patterson-Keels LM, Selvaggi SM, Haefner HK, Randolph Jr JF. Morphologic assessment of endometrium overlying submucosal leiomyomas. J Reprod Med. 1994;39(8):579–84.
2. Al-Hendy A, Salama SA. Catechol-O-methyltransferase polymorphism is associated with increased uterine leiomyoma risk in different ethnic groups. J Soc Gynecol Investig. 2006;13(2):136–44.
3. Tsibris JC, Segars J, Coppola D, Mane S, Wilbanks GD, O'Brien WF, et al. Insights from gene arrays on the

development and growth regulation of uterine leiomyomata. Fertil Steril. 2002;78(1):114–21.
4. Wang H, Mahadevappa M, Yamamoto K, Wen Y, Chen B, Warrington JA, et al. Distinctive proliferative phase differences in gene expression in human myometrium and leiomyomata. Fertil Steril. 2003;80(2): 266–76.
5. Gross K, Morton C, Stewart E. Finding genes for uterine fibroids. Obstet Gynecol. 2000;95(4 Suppl 1):60.
6. Mettler L, Semm K, Gebhardt IH, Schollmeyer TH, Schollmeyer M, Meyer P, et al., editors. Endoskopische Abdominalchirurgie in der Gynäkologie. Stuttgart/ New York: Schattauer; 2002.
7. Mettler L, Semm K, Schollmeyer TH, Schollmeyer M, Meyer P, Ternamian A, editors. Manual for laparoscopic and hysteroscopic gynecological surgery. New Delhi: Jaypee Brothers Medical Publishers LTD; 2006.
8. Schollmeyer TH, Mettler L, Rüther D, Alkatout I, editors. Practical manual for laparoscopic and hysteroscopic gynecological surgery. New Delhi/ Panama City/London/Philadelphia: Jaypee Brothers Medical Publishers; 2013.
9. Bulletti C, De Ziegler D, Polli V, Flamigni C. The role of leiomyomas in infertility. J Am Assoc Gynecol Laparosc. 1999;6(4):441–5.
10. Hunt JE, Wallach EE. Uterine factors in infertility – an overview. Clin Obstet Gynecol. 1974;17(4):44–64.
11. Buttram Jr VC, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril. 1981;36(4):433–45.
12. Vollen-Hoven BJ. Uterine fibroids: a clinical review. Br J Obstet Gynaecol. 1990;97:285–8.
13. Deligdish L, Loewenthal M. Endometrial changes associated with myomata of the uterus. J Clin Pathol. 1970;23(8):676–80.
14. Verkauf BS. Myomectomy for fertility enhancement and preservation. Fertil Steril. 1992;58(1):1–15.
15. Robert HG. Prècis de gynecologie. Paris: Masson; 1974.
16. Ben-Nagi J, Miell J, Mavrelos D, Naftalin J, Lee C, Jurkovic D. Endometrial implantation factors in women with submucous uterine fibroids. Reprod Biomed Online. 2010;21(5):610–5.
17. Klatsky PC, Lane DE, Ryan IP, Fujimoto VY. The effect of fibroids without cavity involvement on ART outcomes independent of ovarian age. Hum Reprod. 2007;22(2):521–6.
18. Sunkara SK, Khairy M, El-Toukhy T, Khalaf Y, Coomarasamy A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum Reprod. 2010;25(2):418–29.
19. Oliveira FG, Abdelmassih VG, Diamond MP, Dozortsev D, Melo NR, Abdelmassih R. Impact of subserosal and intramural uterine fibroids that do not distort the endometrial cavity on the outcome of in vitro fertilization-intracytoplasmic sperm injection. Fertil Steril. 2004;81(3):582–7.
20. Check JH, Choe JK, Lee G, Dietterich C. The effect on IVF outcome of small intramural fibroids not compressing the uterine cavity as determined by a prospective matched control study. Hum Reprod. 2002;17(5):1244–8.
21. Yan L, Ding L, Tang R, Chen ZJ, Li C, Wang Y. Effect of fibroids not distorting the endometrial cavity on the outcome of in vitro fertilization treatment: a retrospective cohort study. Fertil Steril. 2014;101(3):716–21.
22. Somigliana E, De Benedictis S, Vercellini P, Nicolosi AE, Benaglia L, Scarduelli C, et al. Fibroids not encroaching the endometrial cavity and IVF success rate: a prospective study. Hum Reprod. 2011; 26(4):834–9.
23. He Y, Zeng Q, Dong S, Qin L, Li G, Wang P. Associations between uterine fibroids and lifestyles including diet, physical activity and stress: a casecontrol study in China. Asia Pac J Clin Nutr. 2013;22: 109–17.
24. Dandolu V, Singh R, Lidicker J, Harmanli O. BMI and uterine size: is there any relationship? Int J Gynecol Pathol. 2010;29(6):568–71.
25. Marret H, Fritel X, Ouldamer L, Bendifallah S, Brun JL, De Jesus I, et al. Therapeutic management of uterine fibroid tumors: updated French guidelines. Eur J Obstet Gynecol Reprod Biol. 2012;165(2): 156–64.
26. Ezzati M, Norian JM, Segars JH. Management of uterine fibroids in the patient pursuing assisted reproductive technologies. Womens Health (Lond Engl). 2009;5(4):413–21.
27. Li TC, Mortimer R, Cooke ID. Myomectomy: a retrospective study to examine reproductive performance before and after surgery. Hum Reprod. 1999;14(7): 1735–40.
28. Vercellini P, Maddalena S, De Giorgi O, Pesole A, Ferrari L, Crosignani PG. Determinants of reproductive outcome after abdominal myomectomy for infertility. Fertil Steril. 1999;72(1):109–14.
29. Seracchioli R, Rossi S, Govoni F, Rossi E, Venturoli S, Bulletti C, et al. Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy. Hum Reprod. 2000;15(12):2663–8.
30. Dubuisson JB, Fauconnier A, Deffarges JV, Norgaard C, Kreiker G, Chapron C. Pregnancy outcome and deliveries following laparoscopic myomectomy. Hum Reprod. 2000;15(4):869–73.
31. Harris WJ. Uterine dehiscence following laparoscopic myomectomy. Obstet Gynecol. 1992;80(3 Pt 2): 545–6.
32. Mecke H, Wallas F, Brocker A, Gertz HP. Pelviscopic myoma enucleation: technique, limits, complications. Geburtshilfe Frauenheilkd. 1995;55(7):374–9.
33. Friedmann W, Maier RF, Luttkus A, Schafer AP, Dudenhausen JW. Uterine rupture after laparoscopic myomectomy. Acta Obstet Gynecol Scand. 1996; 75(7):683–4.
34. Pelosi 3rd MA, Pelosi MA. Spontaneous uterine rupture at thirty-three weeks subsequent to previous superficial laparoscopic myomectomy. Am J Obstet Gynecol. 1997;177(6):1547–9.

35. Foucher F, Leveque J, Le Bouar G, Grall J. Uterine rupture during pregnancy following myomectomy via coelioscopy. Eur J Obstet Gynecol Reprod Biol. 2000;92(2):279–81.
36. Hockstein S. Spontaneous uterine rupture in the early third trimester after laparoscopically assisted myomectomy. A case report. J Reprod Med. 2000;45(2): 139–41.
37. Seinera P, Arisio R, Decko A, Farina C, Crana F. Laparoscopic myomectomy: indications, surgical technique and complications. Hum Reprod. 1997;12(9): 1927–30.
38. Darai E, Dechaud H, Benifla JL, Renolleau C, Panel P, Madelenat P. Fertility after laparoscopic myomectomy: preliminary results. Hum Reprod. 1997;12(9): 1931–4.
39. Ribeiro SC, Reich H, Rosenberg J, Guglielminetti E, Vidali A. Laparoscopic myomectomy and pregnancy outcome in infertile patients. Fertil Steril. 1999;71(3): 571–4.
40. Arthur R, Kachura J, Liu G, Chan C, Shapiro H. Laparoscopic myomectomy versus uterine artery embolization: long-term impact on markers of ovarian reserve. J Obstet Gynaecol Can. 2014;36(3):240–7.
41. Gizzo S, Saccardi C, Patrelli TS, Ancona E, Noventa M, Fagherazzi S, et al. Magnetic resonance-guided focused ultrasound myomectomy: safety, efficacy, subsequent fertility and quality-of-life improvements, a systematic review. Reprod Sci. 2014;21(4):465–76.
42. Donnez J, Tomaszewski J, Vazquez F, Bouchard P, Lemieszczuk B, Baro F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med. 2012;366(5):421–32.
43. Tinelli A, Malvasi A, Cavallotti C, Dell'Edera D, Tsin DA, Stark M, et al. The management of fibroids based on immunohistochemical studies of their pseudocapsules. Expert Opin Ther Targets. 2011;15(11): 1241–7.
44. Youngs LA, Taylor HB. Adenomatoid tumors of the uterus and fallopian tube. Am J Clin Pathol. 1967;48(6):537–45.
45. Tiltman AJ. Adenomatoid tumours of the uterus. Histopathology. 1980;4(4):437–43.
46. Nogales FF, Isaac MA, Hardisson D, Bosincu L, Palacios J, Ordi J, et al. Adenomatoid tumors of the uterus: an analysis of 60 cases. Int J Gynecol Pathol. 2002;21(1):34–40.
47. Hes O, Perez-Montiel DM, Alvarado Cabrero I, Zamecnik M, Podhola M, Sulc M, et al. Thread-like bridging strands: a morphologic feature present in all adenomatoid tumors. Ann Diagn Pathol. 2003;7(5): 273–7.
48. Di Stefano D, Faticanti Scucchi L, Covello R, Martinazzoli A, Meli C, Bosman C. Uterine diffuse adenomatoid tumor. Does it represent a different biological entity? Gynecol Obstet Invest. 1998;46(1): 68–72.
49. Kalidindi M, Odejinmi F. Laparoscopic excision of uterine adenomatoid tumour: two cases and literature review. Arch Gynecol Obstet. 2010;281(2):311–5.
50. Golden A, Ash JE. Adenomatoid tumors of the genital tract. Am J Pathol. 1945;21(1):63–79.
51. Lee Jr MJ, Dockerty MB, Thompson GJ, Waugh JM. Benign mesotheliomas (adenomatoid tumors) of the genital tract. Surg Gynecol Obstet. 1950;91(2): 221–31.
52. Irikoma M, Takahashi K, Kurioka H, Miyazaki K, Kamei T. Uterine adenomatoid tumors confirmed by immunohistochemical staining. Arch Gynecol Obstet. 2001;265(3):151–4.
53. Tiltman A. Adenomatoid tumors of the uterus. Int J Gynecol Pathol. 2002;21(3):305; author reply.
54. Agbata AI, Kovi J. Adenomatoid tumor of the uterus. Report of two cases. J Natl Med Assoc. 1975;67(6): 447–9.
55. Bisset DL, Morris JA, Fox H. Giant cystic adenomatoid tumour (mesothelioma) of the uterus. Histopathology. 1988;12(5):555–8.
56. Saran M, Sanghi A, Faruqi A. Adenomatoid tumour of the uterus presenting as cyst. J Obstet Gynaecol. 2007;27(6):637–8.
57. Mitsumori A, Morimoto M, Matsubara S, Yamamoto M, Akamatsu N, Hiraki Y. MR appearance of adenomatoid tumor of the uterus. J Comput Assist Tomogr. 2000;24(4):610–3.
58. Cheng CL, Wee A. Diffuse uterine adenomatoid tumor in an immunosuppressed renal transplant recipient. Int J Gynecol Pathol. 2003;22(2):198–201.
59. Salazar H, Kanbour A, Burgess F. Ultrastructure and observations on the histogenesis of mesotheliomas, "adenomatoid tumors", of the female genital tract. Cancer. 1972;29(1):141–52.
60. Lehto VP, Miettinen M, Virtanen I. Adenomatoid tumor: immunohistological features suggesting a mesothelial origin. Virchows Arch B Cell Pathol Incl Mol Pathol. 1983;42(2):153–9.
61. Quigley JC, Hart WR. Adenomatoid tumors of the uterus. Am J Clin Pathol. 1981;76(5):627–35.
62. Genazzani AR, Brincat M, editors. Frontiers in gynecological endocrinology. Cham: Springer International Publishing; 2014.
63. Nisolle M, Gillerot S, Casanas-Roux F, Squifflet J, Berliere M, Donnez J. Immunohistochemical study of the proliferation index, oestrogen receptors and progesterone receptors A and B in leiomyomata and normal myometrium during the menstrual cycle and under gonadotrophin-releasing hormone agonist therapy. Hum Reprod. 1999;14(11):2844–50.
64. Mettler L, editor. Manual of new hysterectomy techniques. New Delhi: Jaypee Brothers Medical Publishers; 2007.

Uterine Fibroid Pseudocapsule

6

Andrea Tinelli and Antonio Malvasi

Introduction

Uterine myomas or fibroids are the most common benign tumors of the genital organs of women, with a frequent negative impact on reproductive system. They can be single or multiple, and frequently cause of significant female morbidity for interference on the of quality of life [1]. Literature data show that 5.4–77 % of women have myomas, depending either on the study population or by diagnostic techniques applied to myoma detecting [2]. The myoma prevalence is somewhat lower in Europe than in the United States, which are more influenced by racial differences [3]. They are detected in 70 % of uteri after hysterectomy (more than 80 % of cases in the form of multiple myomas) [4]. On 100 total hysterectomy, specimens performed at a distance of 2 mm demonstrated myomas in 73 % of samples of the uterus in premenopausal women and 84 % of the uterus in postmenopausal women. The average number of myomas in this study was 7.6 % among premenopausal women and 4.2 % in postmenopausal women [4]. Previous epidemiological studies, focusing mostly on symptomatic women, largely underestimated myoma prevalence. Fibroids consist mainly of smooth muscle cells (Fig. 6.1) with different amounts of fibrous tissue so, generally, they are benign with few symptoms, but when they disrupt the uterine functions, they cause: excessive uterine bleeding, anemia, defective implantation of an embryo, recurrent pregnancy loss, preterm labor, obstruction of labor, pelvic discomfort, and urinary incontinence and may mimic or mask malignant tumors [5]. Larger fibroids (Fig. 6.2) can even compress any of the surrounding organs, leading to urinary, digestive or sexual symptoms [6].

Several treatments are available to remove fibroids and alleviate symptoms, such as conservative surgery [7], medical therapy [8], or various novel radiological interventions [9]. Despite the frequency with which fibroids are diagnosed and treated, there remains considerable uncertainty and controversy

A. Tinelli, MD (✉)
Gynecology and Obstetric, Vito Fazzi Hospital, Lecce, Italy

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia
e-mail: andreatinelli@gmail.com; andrea.tinelli@unisalento.it

A. Malvasi, MD
Obstetric and Gynecology, Santa Maria Hospital, Bari, Italy

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia
e-mail: antoniomalvasi@gmail.com

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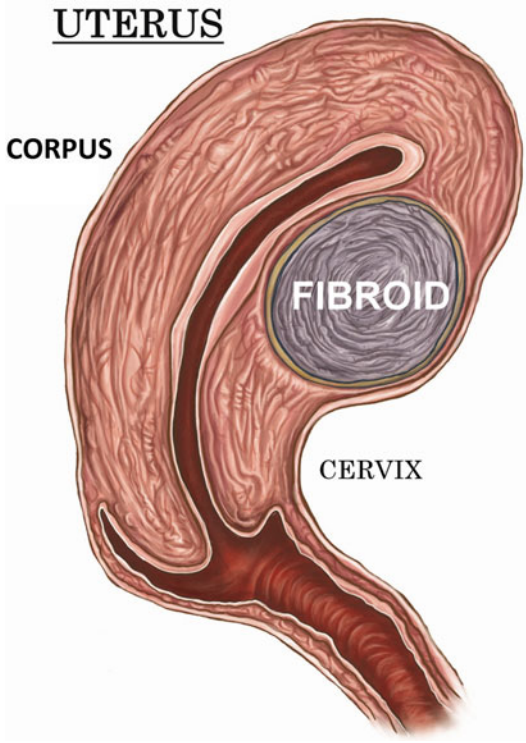

Fig. 6.1 Uterine section showing an intramural fibroid in uterine body

among clinicians and women regarding the best way to manage them.

The problem of uncertain management is also due to interference which causes the fibroid on the myometrium. During its growth, fibroid causes compressive phenomena on the surrounding myometrium, that for ischemic phenomena, produce a sort of pseudocapsule, constituted by a surrounding network of collagen fibers, neurofibers and blood vessels, as a separate fibroneurovascular tissue (Fig. 6.3) [10].

Occasionally the pseudocapsule surface is interrupted by collagen fibers and vessels that anchor the fibroid to myometrium, well represented in microscopic sections (Fig. 6.4). It allows a constitution of a macroscopically clear cleavage plane between fibroid and the pseudocapsule, and between the pseudocapsule and the surrounding myometrium (Fig. 6.5) [11]. The pseudocapsule allows to fibroid only a displacement action (but not destructive) on myometrium, retaining the integrity and contractility of uterine structure [12].

In this chapter we will discuss the importance of this small structure in the context of the myometrium, for the purpose anatomical, pathophysiological and reproductive systems.

Anatomy of Fibroid Pseudocapsule

Microscopically, the pseudocapsule seems to be as a continuous layer between the fibroid and myometrium and is made of a thickening of collagen fibers and blood vessels that form a vascular ring, sonographically called "ring of fire" by echo-color Doppler: the pseudocapsule is separated from the surrounding myometrium, sonographically forming a hyperechogenic ring that surrounds and defines myoma (Fig. 6.6) [10]. To help with understanding of the microneuroanatomy of the fibroid peripheral area, we should get close with the story of pseudocapsule entity. An anatomical textbook, published at the end of last century, asserted: "*myoma shows a nodular aspect, a round image, well circumscribed, to enucleate even if they miss a pseudocapsule*" [13]. These authors confirmed the existence of the fibroid pseudocapsule and cleavage plane to identify and to respect during a myomectomy [14]. The first paper that described a fibrovascular system over a fibroid as "a mass of proliferating arteries" was in 1944 [15] and then, Farrer-Brown in 1970 [16] and Awataguchi in 1982 [17] found a fibrovascular plexus around the periphery of the fibroid. Lately, Casey et al. reported significantly higher microvasculature density in the surrounding myometrium in large fibroids (Fig. 6.7); the author discovered that the vascular capsule was a substantial feature of all fibroids, excluding those smaller, and that it reaches the highest density of blood vessels in large tumors [18]. Pathologists examined the relationship between ultrasound and histological findings of the fibroids vascular capsule in the last century, in a series of women using Gn-RH analogues in preoperative treatment before myomectomy [19–21].

Walocha et al. [22] performed a microstructural evaluation of the fibroid pseudocapsule and found that the density of blood vessels increases

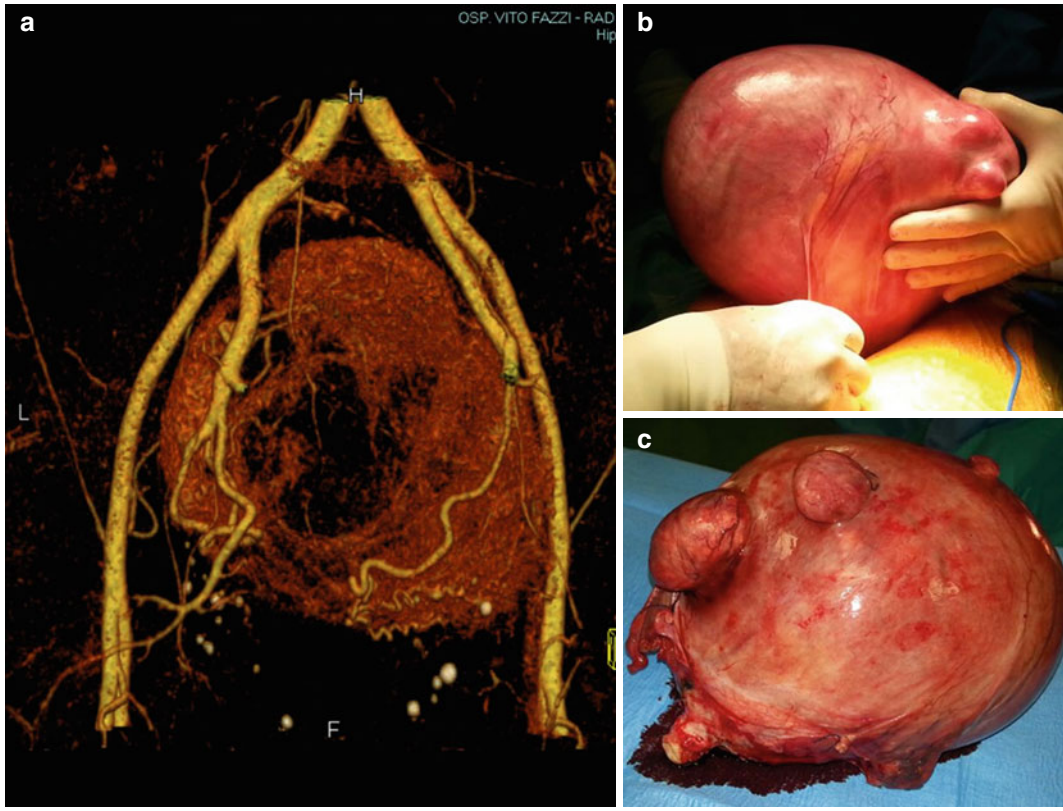

Fig. 6.2 A giant fibroid of 24 cm of diameter: (**a**) an angio-CT reconstruction of the fibroid peripheral vascularization, as a surrounding vascular network; (**b**) laparotomic hysterectomy; (**c**) the uterus on the servant table after surgery

around myoma. As the fibroid grows, new blood vessels penetrate the tumor from its periphery where "the vascular capsule" network is formed. Some of the vessels in the pseudocapsule connect at the base of the myoma and form a little foot which often bleeds during an extra-capsular myomectomy. These authors analyzed the fibroid vascular system using corrosion casting combined with scanning electron microscopy and affirmed that the pre-existing blood vessels undergo in regression and new vessels invade the tumor from the periphery during the development of myomas. Myoma pseudocapsule originates from small vessels entering the tumor from the periphery, forming a "vascular network" around the myoma, with flattened veins compressed by the tumor (Fig. 6.2, image a) [22].

Forssman et al. reported the vascular capsule surrounding myoma of 2 cm of diameter and found that the inner aspect of the capsule contained large vessels that invade the capsule from the periphery [23].

Neurotransmitters in Myoma Pseudocapsule

The fibroid pseudocapsule is a structure which surrounds the uterine fibroid and separates it from the uterine tissue. At the ultrastructural level, visualized by transmission electron microscopy, the pseudocapsule cells have the features of smooth muscle cells similar to the myometrium. So, the pseudocapsules are part of the myometrium which compresses the leiomyoma. This ultrastructural feature suggests that when removing fibroids their pseudocapsules should be preserved to preserve myometrium and post-surgical uterine anatomy [24].

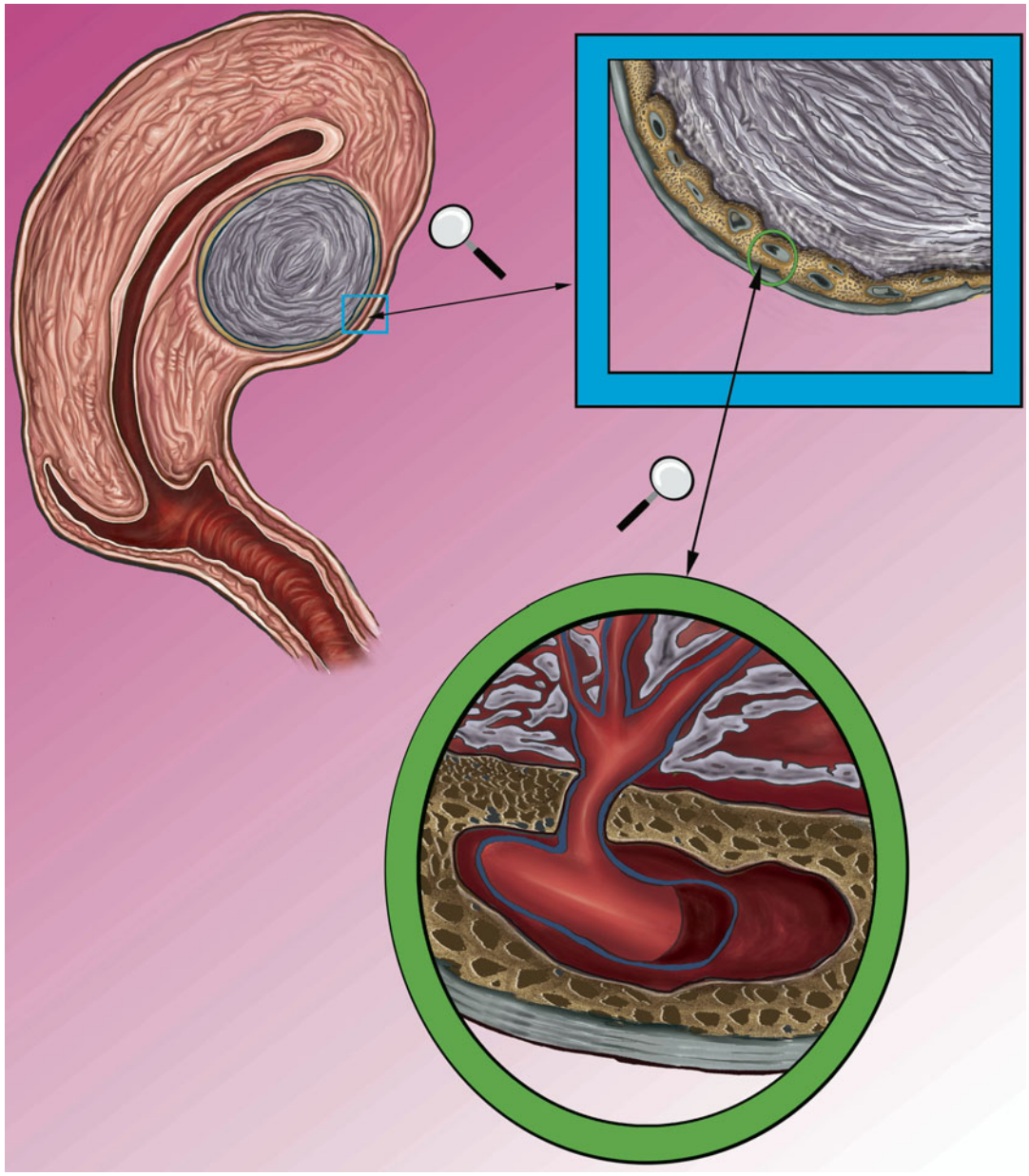

Fig. 6.3 On the *top* of the *left side*, is represented the uterine section of with intramural fibroid; the inset highlights the pseudocapsule, which is magnified on the *right*. *Below* is represented the pseudocapsule in the ring, constituted by a surrounding network of collagen fibers, neurofibers and blood vessels

Wei et al. demonstrated that in large uterine fibroids, the most biologically active zone is the region next to the periphery with a higher level of gene expression, a higher density of blood vessels, a higher proliferative rate, and a lower level of hyaline degeneration [25].

These studies confirms preliminary evidence that pseudocapsules contain neuropeptides together with their related fibers, as a neurovascular bundle, containing a vascular network rich in neurotransmitters like a neurovascular bundle (Fig. 6.8) [26].

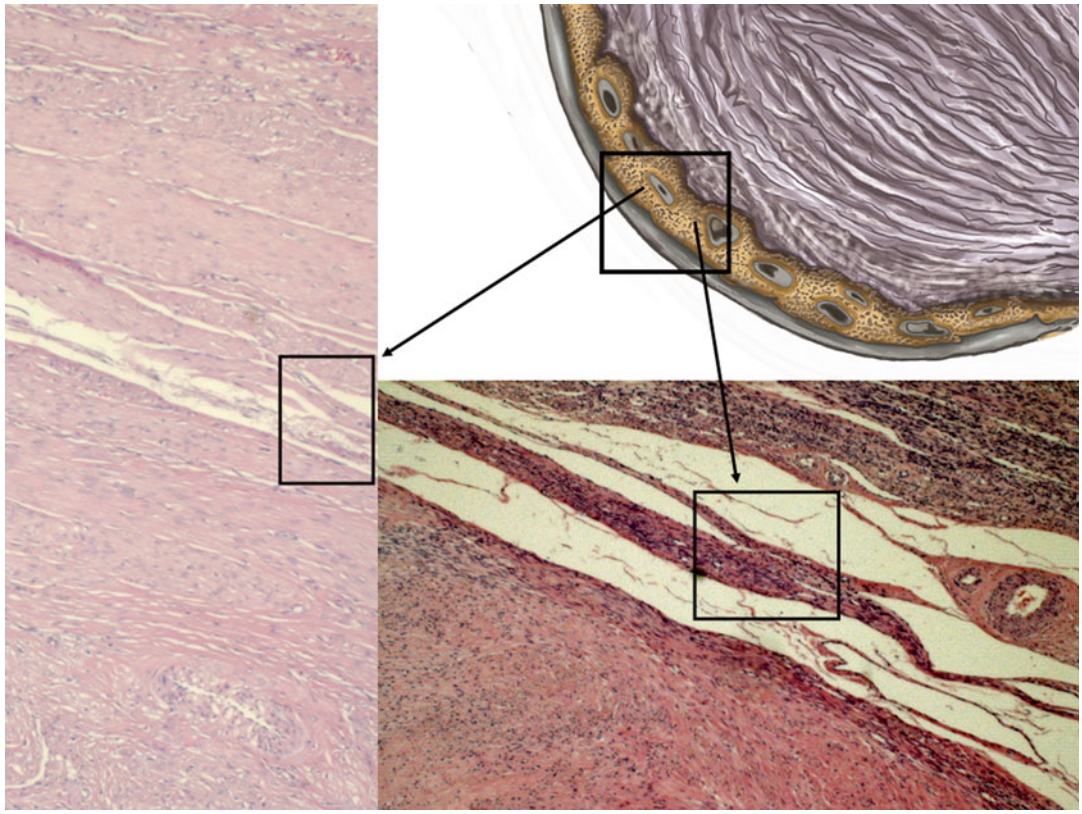

Fig. 6.4 In the drawing of fibroid to the *upper right side*, the pseudocapsule is highlighted into the *box*; to the *left* and *below*, *black arrows* show, in the *two box*, histological microphotographs, stained by hematoxylin & eosin, of myoma pseudocapsule: detection of compressed myometrial muscular smooth tissue, collagen fibers and blood vessels

Literature data confirm that pseudocapsules contain many neuropeptides and neurotransmitters [27–29], physiologically active. Moreover, these substances may play a significant role in wound healing [30–32] and innervation repair [33], and may be essential for reproductive [34–36] and sexual function [37, 38]. Indeed, the lower urinary tract neuropeptide–receptor systems may represent a potential target for therapeutic interventions [39, 40].

Comparison Between Myoma Pseudocapsule and Prostate Capsule

Mettler et al. studied the myoma pseudocapsule by endocrinological side, affirming it has a delicate vascular network rich with neurotransmitters, as a neurovascular bundle containing neuropeptides and related fibers surrounding prostate [26].

The idea of a neurovascular bundle surrounding a myoma, inside pseudocapsule, derives from a multidisciplinary discussion among gynecologists and urologists, on analogies of myoma pseudocapsule with the prostate capsule. Based on the purpose of reducing the probability of impotence associated prostate cancer treatment, urologist generally must preserve neurovascular bundles surrounds prostate. Anatomically, the neurovascular bundles are situated on the peripheral to the prostate. The neurovascular bundles is placed in the lateral pelvic fascia, deep, lateral, and cephalad to Denonvilliers' fascia and the prostatic fascia and the levator fascia [41]. As evidenced by Takenaka et al. [42] and Costello et al. [43], the cavernous branches connect the

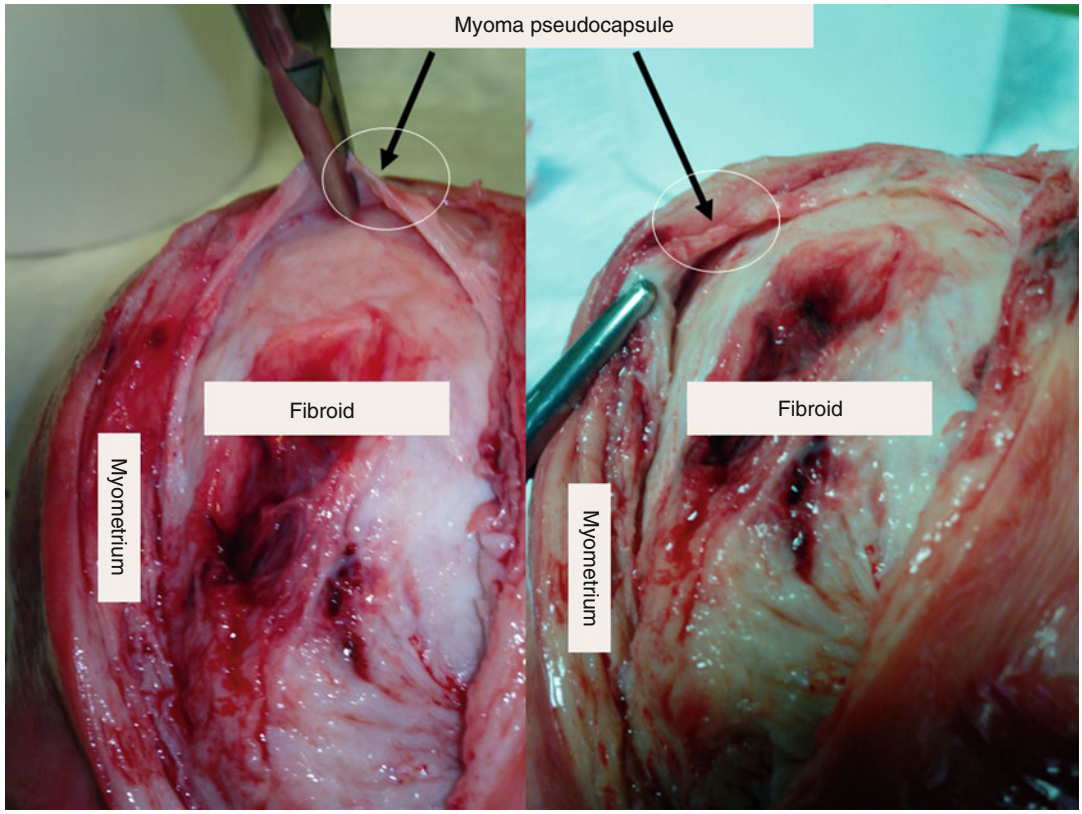

Fig. 6.5 A sectioned uterus with an intramural fibroid; it is macroscopically clear the cleavage plane between fibroid and the pseudocapsule, in the *white ring*, gripped by the forceps

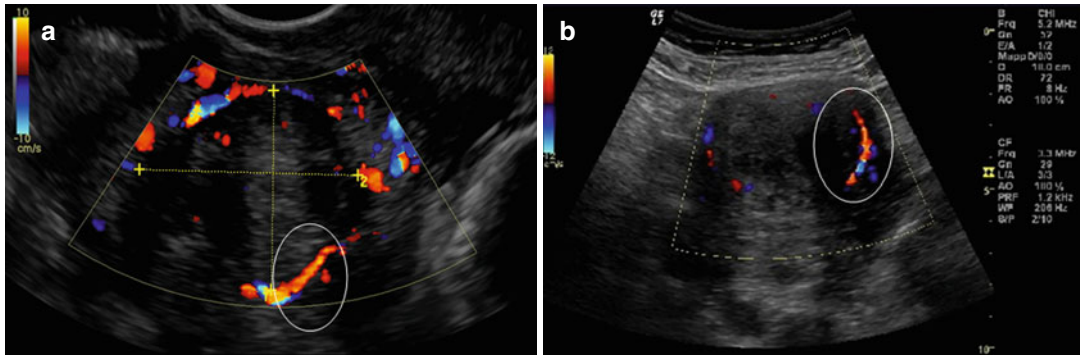

Fig. 6.6 A uterine fibroid Doppler ultrasonography showing, in the *white ring*, the fibroid pseudocapsule as a "ring of fire" around fibroid (**a**, **b**, **d**); in the image (**c**), it is enhanced, in the *white box*, the myoma pseudocapsule as an hyperecogenic *white outline*

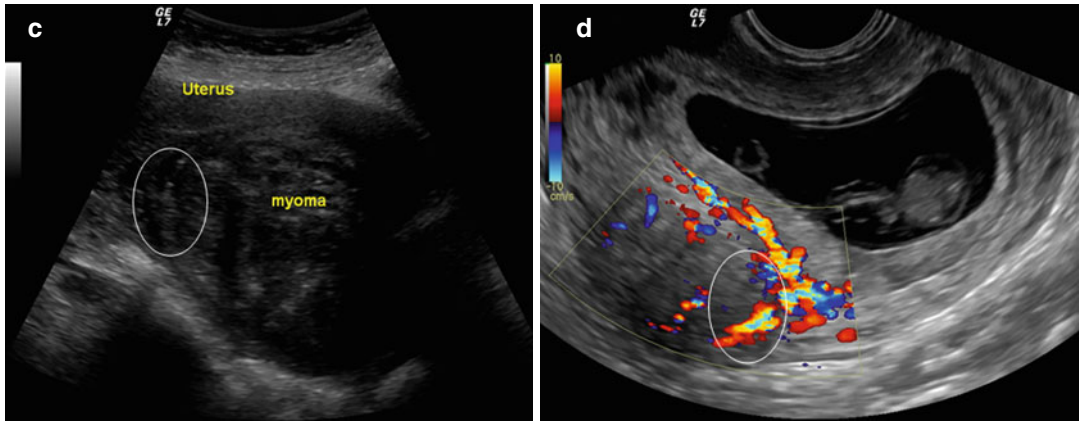

Fig. 6.6 (continued)

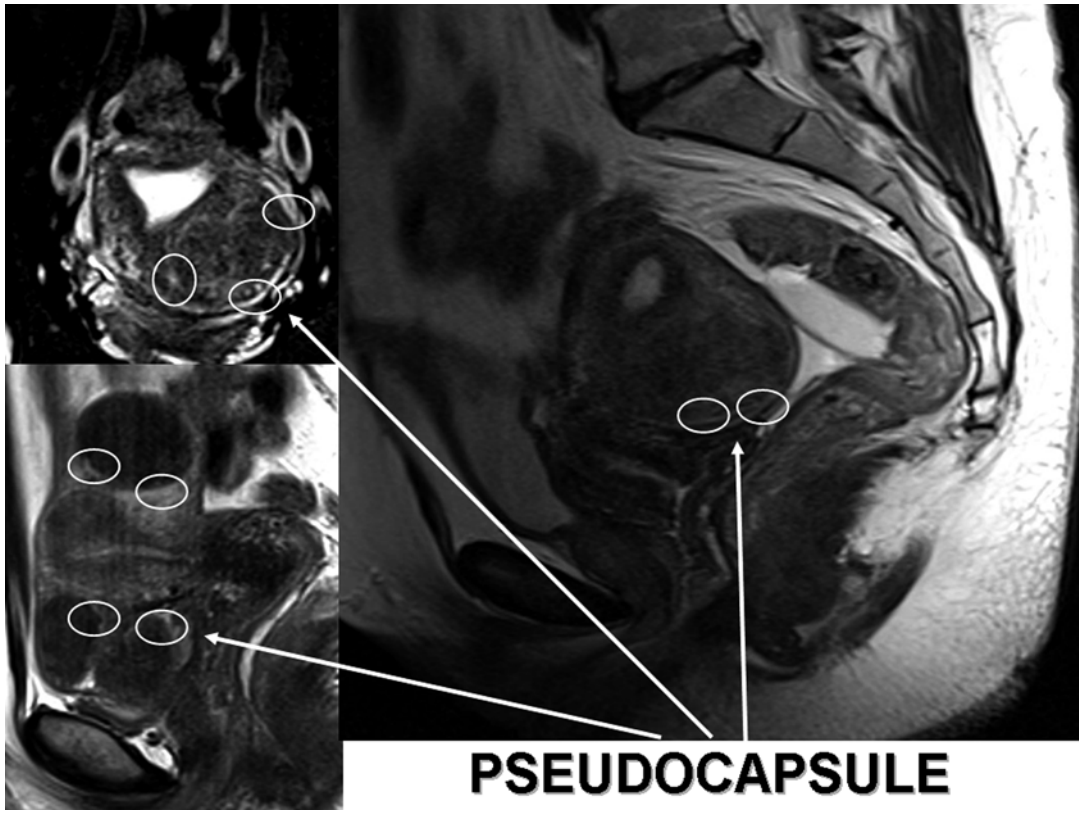

Fig. 6.7 MRI reconstructions of myomatosic uteries. The white arrows indicates white rings enhancing myoma pseudocapsules

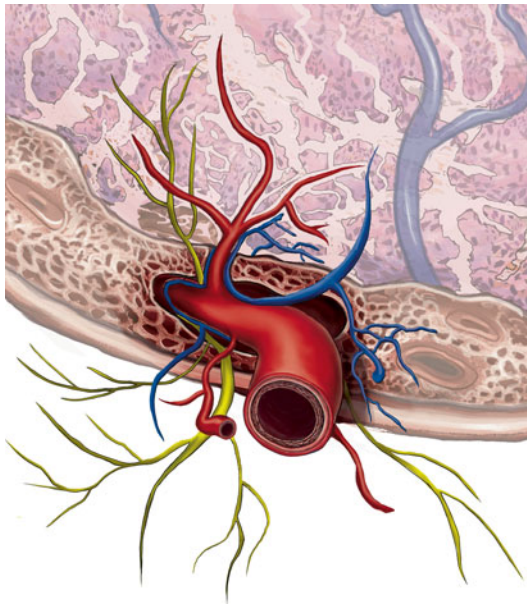

Fig. 6.8 A 3D reconstruction of myoma pseudocapsule as a neurovascular bundle: the fibroneurovascular network surrounding fibroid is rich in neuropeptides and neurotransmitters

capsular arteries and veins in a spray-like distribution to form the neurovascular bundles 20–30 mm distal to the junction of the bladder and prostate. At the apex of the prostate, the branches of the nerves to the cavernous bodies and striated sphincter also have a spray-like distribution both anteriorly and posteriorly with large variation. This anatomical framework has been defined the neurovascular bundles by Walsh [44]. As analyzed by surgeons, the neurovascular bundles passes through two distinct fascial planes that surround the prostate called "the prostatic fascia and levator fascia": the nerves cross in the neurovascular bundle and innervate the corpora cavernosa, rectum, prostate, and levator ani musculature. The last three receive a blood supply from vessels running in the neurovascular bundle. Nowadays, in most men who are candidates for radical prostatectomy, it is usually safe to preserve both neurovascular bundles and rarely necessary to excise both of them. If nerve sparing is performed correctly, the prostatic fascia must remain intact on the prostate. Moreover, when tumor extends through the capsule, it seldom penetrates more than 1–2 mm, this tissue can often be removed likewise, with preservation of the neurovascular bundles. Even in extra-prostatic extension in the region of the neurovascular bundles, it is feasible to partially excise the bundle, preserve potency, and achieve negative margins of excision [45]. The prostatic neurovascular bundle provide both somatic and autonomic innervations to the continence mechanism. The excision of neurovascular bundle causes more incontinence and impotency than when the neurovascular bundles are preserved [46]. In order to spare the prostatic neurovascular bundles, laparoscopic or robotic assisted prostatectomy are both useful [47], since the magnification facilitates a more gentle dissection with less traction and careful dissection [48]. Surgically, a midline vertical incision is made into Denonvilliers' fascia—along the entire gland extending up the urethra—and the fascia is sharply retracted to the right and left to expose the posterior prostatic capsule. This incision must completely release the neurovascular bundles to allow correct restore of the retractor blades and thus to avoid a traction injury to the neurovascular bundles. Blunt or sharp dissection is often needed to release the bundles far enough laterally to achieve adequate exposure to the posterior prostate base. Although these nerves are microscopic [49], their anatomic location can be evaluated intraoperatively through the use of the capsular vessels as a landmark. An opening in the levator fascia is performed by sharp incision along the anterolateral surface of the prostate starting at the base of the prostate and proceeding toward the apex. This maneuver releases the bundle laterally, thus making it easier to make the next step, where the bundle is released posteriorly at the apex. Once the superficial fascia has been released, the site of the neurovascular bundles can be identified by the presence of a thin "groove" on the posterolateral edge of the prostate. The interfascial plane (i.e., between the levator and prostatic fascia) is developed gently using blunt dissection with a fine curved dissector and a gentle diathermocoagulation. Dissection con-

tinues in close approximation to the surface of the prostatic fascia in efforts to optimize quantitative cavernous nerve preservation. If bleeding occurs from periprostatic vessels, insufflation pressure can be in the meanwhile increased and pressure applied to the source of bleeding with hemostatic gauze. Hemostasis with high wattage diathermocoagulation or ultrasonic heat energy should be always avoided during dissection near the neurovascular bundles, as these energy sources have been shown to be injurious to cavernous nerve function in the canine model [50]. The neurovascular bundles may be observed through the use of ultrasound Doppler, which has become an important technique for non-invasive flow measurement in medical applications [51]. On the bases of these findings about the importance of the prostatic capsule and the important and physiologic role of nerve-sparing techniques for prostatectomy, and comparing this structure to the fibroid pseudocapsule, the knowledge of peripheral neurovascular bundle of the uterine leiomyoma was challenged and revisited.

Intracapsular Myomectomy

Fibroids enucleating or myomectomy, the removal of fibroids surgically without hysterectomy, is the second most common surgical procedure for this condition, to restore uterine anatomy [7]. Myomectomy is the most common conservative treatment in gynecology, performed by classical open surgery or, currently, by laparoscopy with a less traumatic fibroid removal and better recovery [7].

Literature showed the possibility to perform myomectomy by removing the fibroid from its surrounding structure, the fibroid pseudocapsule [14, 52, 53], called by authors "intracapsular myomectomy". It performs by stretching and extracting fibroid directly from the surrounding fibromuscular skeleton, breaking up the fibrous bridges.

Researches on pseudocapsule started wit Ito et al., who performed an histopathologic evaluation of uterine fibroid and its pseudocapsule, to determine the scientific reason for less blood loss during a intracapsular myomectomy. They demonstrated how a pseudocapsule is formed by extra-cellular matrix around the myoma, separating fibroid from normal myometrium. The authors sustained that the fibroid is anchored to the pseudocapsule by connective bridges, but lacks its own true vascular pedicle [54]. Also Dapunt et al. showed a vascular network surrounding myoma, as a pseudocapsule, so that if the detachment of the myoma occurring into the pseudocapsule, surgeon has less bleeding during myomectomy [55]. Fox et al. studied fibroids by ultrastructural microscopy and showed an anatomical structure different than the normal myometrium: fibroids had a well-defined regular outline and a surrounding pseudocapsule of compressed muscle fibers [56]. The hypothesis of presence of fibroid pseudocapsule was also asserted by Vizza and Motta, whose demonstrated that the pseudocapsule contains the fibers that tend to bulge out from the surrounding myometrium and have a firm, whorled or trabeculate surface [57]. Furthermore, ultrasonographic evaluations have been performed on myomas and their connecting structures: pseudocapsule appeared as an echogenic line around the myoma, with a wall 1 cm or less, and with reinforcement of distal echoes [58]. Additional histological investigations have been performed on the fibroid vascular pseudocapsule to better understand the role in the modern minimally invasive myomectomy [17]. The macroscopic evaluation of the pseudocapsule and of the adjacent myometrium showed that parallel arrays of extremely dense capillaries and larger vessels form the capsule and this is separated from the myometrial vasculature by a narrow avascular cleft. The pseudocapsule vessels from the surrounding myometrium formed clusters in the center of the vascular network to form a sort of pedicle and the veins surrounding the myoma circulated under the pseudocapsule arranged in a plexus [17, 25]. The main principle of myomectomy is to perform all manipulations as precisely and bloodlessly as possible, and the new surgical technique of intracapsular myomectomy meets this requirement. Nevertheless, the impact of sur-

gical myomectomy differs depending on the technique used [59]. The laparotomic myomectomy is different from the laparoscopic technique, also with same intracapsular method: the laparoscopic access route proved to be the most beneficial. The advantages of the laparoscopic approach are the significantly reduced parameters of both intra- and post-surgical blood loss, decreased bladder pain after Foley removal, the lower number of patients requiring pain relief medication and the shorter hospital stay. In addition, laparoscopic intracapsular myomectomy resulted in slightly improved short-term outcomes in relation to postoperative fever, myometrium scar hematomas, ileus and antibiotic treatment compared to open surgery. Finally, the laparoscopic myomectomy has a favorable impact on blood loss by intracapsular method, aiming to preserve musculature under hysterotomy. The CO_2 insufflation can influence blood loss during intracapsular myomectomy, as the increased intra-peritoneal pressure can lead to the occlusion of the small blood vessels and capillaries of the pseudocapsule. This effect, combined with less traumatic endoscopic micro-manipulations, could result in beneficial outcomes of surgery [59].

To better clarify these results, we remember that our intracapsular myomectomy was standardized and published [53]. Laparoscopic myomectomies are performed under general anesthesia by endotracheal intubation with a standardized four port approach: one port for the laparoscope and three lower quadrant ancillary ports (one suprapubic central 10 mm port and two lateral 5 mm ports). The 10 mm central suprapubic port is often changed to 15–20 mm for the introduction of the morcellator at the end of the procedure. All patients receive an intrauterine manipulator prior to laparoscopy, to better mobilize uterus. Intracapsular laparoscopic myomectomy of sub mucous and intramural fibroids is generally performed without injection of ischemic solution into the myometrium. The visceral peritoneum is incised in the midline longitudinal plane, by monopolar scissors or crochet needle electrode, proceeding in depth into myometrium to reach the right plane under myometrium, to detect myoma pseudocapsule with the fibroid below.

Once identified the myoma pseudocapsule, it is well exposed by atraumatic clamp or by irrigator cannula, to provide a panoramic laparoscopic view of pseudocapsule of all subserous-intramural leiomyomas. Then surgeon affects the pseudocapsule by a longitudinal cut, performed by monopolar scissors or Hook electrode at low wattage (30 W), to expose the myoma surface. Then fibroid is hooked by a myoma screw or Collins laparoscopic forceps to perform the traction necessary for its gentle enucleating, helping by irrigator cannula to be inserted in the space under myoma pseudocapsule and fibroid. Hemostasis of the small vessels bleeding is selectively achieved by a low wattage bipolar clamp or by Hook electrode or monopolar scissors, always at 30 W, to free the base of the myoma and the connective bridges from the pseudocapsule (Fig. 6.9). In such way, complete minimal traumatic fibroid removal from its pseudocapsule was accomplished with a minimal blood loss and pseudocapsule sparing. In case of pseudopedunculated myomas, the pedicle is coagulated by bipolar forceps and cut by laparoscopic scissors or cut after placement of loops or staples, without suturing. In cases of deep intramural myomas, chromopertubation is always applied via a cervical cannula not only to check tubal patency but also to facilitate the direct recognition of an inadvertently opened uterine cavity.

The myometrium closuring is performed by a single (for subserous fibroids) or double layer (for intramurals), including overlying serosa, with a round CT-1 curved needle, using intra or extracorporeal knots. In sub-serosal myomectomies, the edges of the uterine defect were approximated with introflecting U-inverted stitches (myometrium/serosa-serosa/myometrium direction) with intra myometrial knot, at 1 cm increments from the edge of the incision (as a "baseball-type" suture). The closure was by surgeon choice: interrupted closure or traditional unidirectional running suture, stared at the end of one of hysterotomic sides.

Deep intramural fibroids required a two-layer myometrial closure with introflecting sutures, ever by a "baseball-type" suture. If the uterine cavity was accidentally opened during fibroid enucleating,

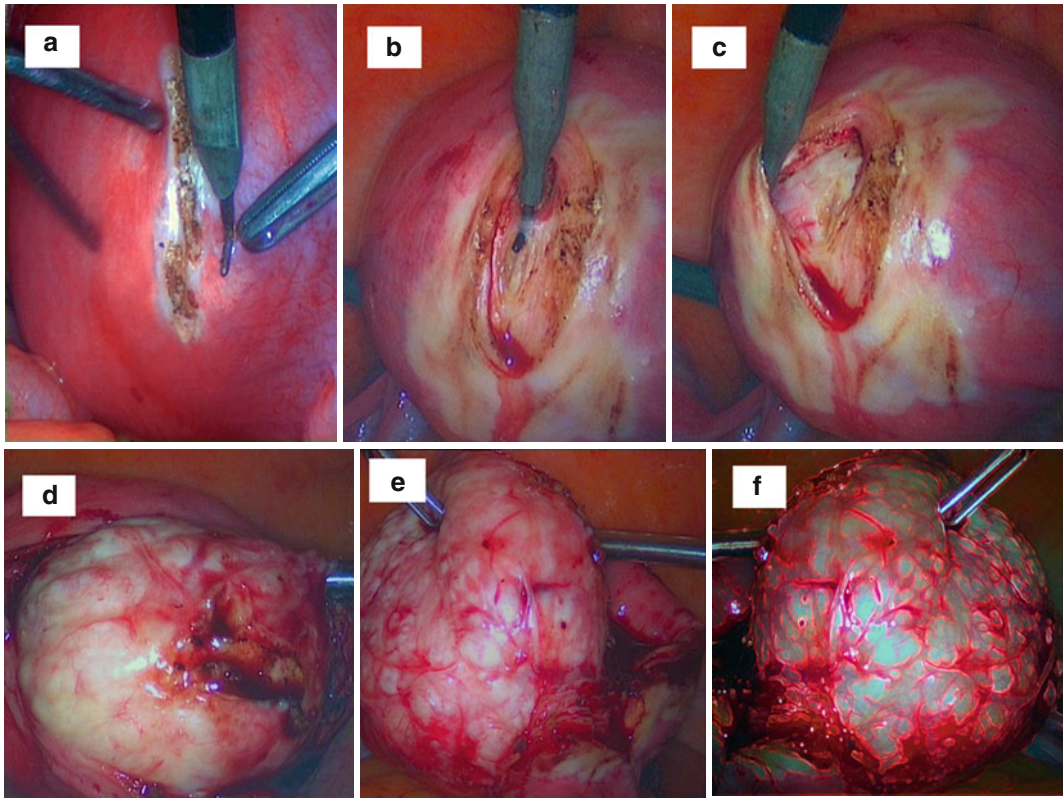

Fig. 6.9 An intraoperative sequence of laparotomic myomectomy images evidencing fibroid pseudocapsule during myoma stretching by surgeon from myometrium: (**a**) the uterine serosa is plotted by a Hook electrode at low wattage (30 W); (**b**) the vertical cut proceeds in depth up to the fibroid, cutting gently the pseudocapsule (always by low wattage energy) to expose the myoma surface; (**c**) surgeon expose the fibroid with a lateralization and sparing of the pseudocapsule during myoma removal; (**d**) after inserting a mini-drill in fibroid, the surgeon gently pulls the fibroid, with its enucleation from the uterine fovea; (**e**) when exposed to the fibroid, the surgeon show the residual branches of pseudocapsule connecting fibroid to uterus, to be cut with scissors or by Hook electrode; (**f**) the fibroid is enucleated; residues of fibrous strands, cut during myomectomy, appear on fibroid surface

2–3 deep myometrial single or continuous sutures were applied on the uterine cavity edges. After hysterorraphy, fibroids are usually morcellated.

The Functional Autonomy of Pseudocapsule and Its Impact on Muscular Healing

The biochemical growth factors evaluated in the pseudocapsule vessels cause intense angiogenesis in pseudocapsule, probably promoted by the fibroids [60]. The angiogenesis of the myoma pseudocapsule likely leads to the formation of a "protective" vascular capsule responsible for the supply of blood to the growing tumor [61]. However, studies demonstrated a dysregulation of various growth factors and their receptors in uterine myomas [17, 61].

In fact, a research on gene expression analysis in uterine leiomyoma pseudocapsule revealed an angiogenic profile in pseudocapsule [60]. In this investigation authors performed, by quantitative real-time RT-PCR method (qRT-PCR), a gene expression analysis of PC, matching it with the same analysis in UL and UM, evaluating the expression levels of IGF-2, used as tumoral marker, and COL4A2, CYR61/CCN1, CTGF/CCN2, VEGF-A and vWF, known to be involved in angiogenic processes.

The results clearly indicated that the pseudocapsule was a structure anatomically distinguishable from the myometrium and the surrounding fibroid, displaying a significant and specific gene expression profile. The pseudocapsule, as the fibroid, exhibited a significantly reduced expression of the IGF-2 gene, known to be a tumor growth marker, if compared to the fibroid, suggesting that it has a non-fibroid origin and that it has a structural continuity with myometrium. The pseudocapsule also showed a statistical relevant over-expression of the endoglin/CD105 gene, when compared to the myometrium and to the fibroid. Based on these evidences, the over-expression of the endoglin gene, rather than of other angiogenic genes, seemed to indicate the presence of an active angiogenesis correlated with reparative process in the pseudocapsule. All together these data clearly depicted the pseudocapsule as a site of intense angiogenesis linked to the endoglin activation rather than other angiogenic factors such as VEGF-A or vWF. The presence of an active angiogenesis is concordant with the histological studies that describe a parallel array of extremely dense capillaries in the pseudocapsule and in the adjacent myometrium, that are absent in fibroid. This can define the structural and functional features of pseudocapsule, that could explain its possible roles in the uterine regenerative process [62].

Moreover, in such regenerative process, there is also the involvement of neuropeptides and neurotransmitters, extremely important in wound healing. In fact, there is evidence that the nervous system and its neurotransmitters, such as Substance P (SP), Vasoactive Intestinal Peptide (VIP), neuropeptide Y (NPY), Oxytocin, Vasopressin (VP), PGP9.5, calcitonin gene-related peptide (CGRP), growth hormone-releasing hormone (GHRH), play a role in mediating inflammation and healing [62–64]. Referring to uterine musculature scar physiology, these peptides sparing enhances a correct healing of an hysterotomy, as evidenced by Mettler et al. [26].

Most of these neuropeptides have been highlighted in the pseudocapsule.

Malvasi et al. [27] evaluated the distribution of two neuropeptides, the SP and the VIP in pseudocapsule of uterine fibroids: they proved that these neurofibers are present in the pseudocapsule of the fibroid as well as in the normal myometrium of the non-pregnant uterus [27].

Then, Malvasi et al. [28] showed also the presence of NT, NPY and PGP 9.5 presence in myometrium as well as in fibroid pseudocapsule, underlying their possible impact on muscular physiology. Finally, the same authors [29] evaluated the opioid neuropeptides, as enkephalin (ENK) and oxytocin (OXT), in the nerve fibers within pseudocapsule and their possible influence in human reproduction. An absence of ENK-positive nerve fibers was seen in the uterine fundus and corpus fibroid pseudocapsules, whereas they were observed in the nerve fibers in fibroid pseudocapsules obtained from the isthmian–cervical region. OXT-positive fibers were present in fibroid pseudocapsules of all uterine regions, whereas the distribution of OXT-positive fibers was significantly higher in the isthmian–cervical region. Authors speculated that ENK- and OXT-positive nerve fibers are present mainly in the isthmian–cervical pseudocapsules (Fig. 6.10) than in the corporal pseudocapsules [29]. The present findings are important to discern the pathophysiology of the female reproductive system and sexual disorders manifesting after surgical procedures in the cervix, including complications during pregnancy and delivery (i.e. miscarriage and cervical dystocia during labor).

As the neuropeptides are transported to the tissues by the neurovascular network, the myoma pseudocapsule, as neurovascular bundle [26], is therefore a structure rich of neuropeptides. Pseudocapsule vessels were also studied by a preliminary three-dimensional mathematical model [65], who showed an increase vascular tortuosity, disarray, an abnormal branching and the presence of “cul-de-sac” pseudocapsule vessels. All of these features are similar to malignant neoplastic tissue vessels features, present in malignant tumors. It was not possible to clarify if the pseudocapsule vasculature network could be sustained by mechanical and inflammatory effects of myoma on myometrium, or produced by a sort of neoangiogenesis “neoplastic-type”, due to the

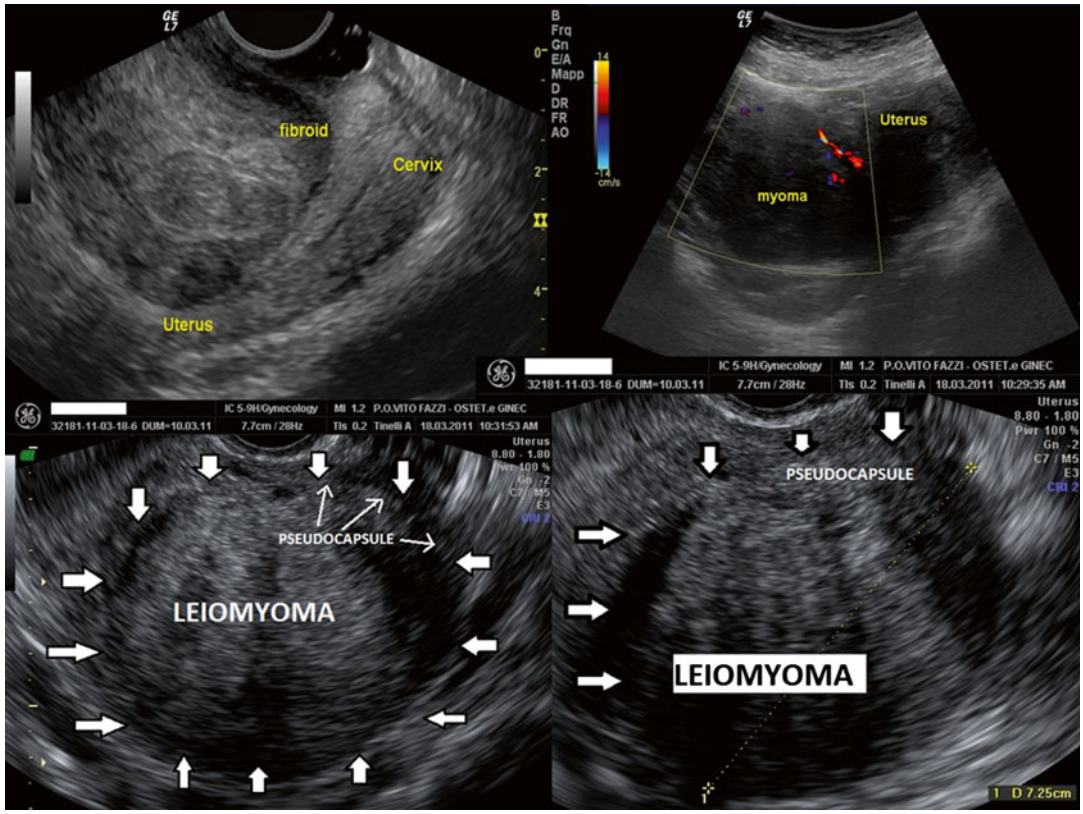

Fig. 6.10 The ultrasonographic figure shows isthmian–cervical pseudocapsules, rich of ENK-positive and OXT-positive nerve fibers

fibroid growth or even to a muscle and tissue healing process, such as a neurovascular preparative reaction of female body to a fibroid expulsion (pedunculated fibroids), necrosis or degeneration, allowing a normal uterine restoration [65].

In human body, difficulties in obtaining serial samples of the hysterotomic scar during myomectomy or cesarean section, are a major barrier to our understanding of the events involved in the post-myomectomy and post-cesarean section remodeling processes of the uterine wound. They can be only monitored by ultrasound or MRI [30].

However, irrespective of the ultimate result, wound healing is a dynamic, interactive process involving neuromediators, angiogenetic factors, neuropeptides, blood cells, extracellular matrix, and parenchymal cells that follows three complex and overlapping phases: inflammation, tissue formation, and tissue remodeling [66]. And this healing process is be involved also for post-operative adhesion development, as consequence of myomectomy and associated with a high risk of de-novo adhesion formation, that may ever decrease fertility [67].

About adhesions' formation after myomectomy, authors applied their surgical method on a large series of patients, valuating adhesions following intracapsular laparoscopic and abdominal myomectomy with or without an anti-adhesion barrier, using non-systematic second look surgery [11]. When an adhesion barrier was not used, there was a significant rate of adhesions in laparotomy (28.1 %) compared to laparoscopy (22.6 %). Filmy and organized adhesions were predominant with an adhesion barrier, and cohesive adhesions were more common without an adhesion barrier. Basing on these dates, the adhesion barrier should be suggested after laparoscopic intracapsular myomectomy in

women searching pregnancy, since it appears to promote a correct healing, reducing the adhesion formation.

The Advantage of Endoscopically Tailored Myomectomy and Prostatectomy

The radical prostatectomy must be balanced between achieving cancer control (negative surgical margins) and preservation of the neurovascular bundle to spare sexual function and post-surgical function. This can be accomplished by an endoscopically tailored micro-surgery, which spares nerve injuries. Likewise, myomectomy should be performed by an intracapsular method, since the uterus is fully innerved and each myomectomy site could lead to uterine neuro-anatomical damage.

Revisiting pelvic innervations in both men and women, it is derived from the superior hypogastric plexus, sympathetic chain, parasympathetic fibers (S2-4) and the sacral plexus (S1-S5). The superior hypogastric plexus is the downward continuation of the inferior mesenteric plexus over the lower aorta and sacral promontory. Right and left hypogastric nerves supply the inferior hypogastric plexi over the posterior-lateral pelvis, passing behind the common iliac arteries before entering the utero-sacral and cardinal ligaments. In women, this system innervates the uterus and upper vagina. The uterus receives its primary innervations from the utero-vaginal plexus (Frankenhauser's plexus), which is located near the transverse cervical ligament lateral to the cervix. Nerve fibers are distributed throughout the myometrium with the branches of the uterine artery. There are nerve fibers throughout the basal third of the endometrium and a significant plexus at the endometrial-myometrial interface [68].

Basing on these neuroanatomical findings, authors developed and standardized their intracapsular myomectomy technique [52] as urologists standardized their prostatectomy, both neurovascular bundle sparing (Fig. 6.11). The presence of neurotransmitters in the fibroid pseudocapsule, as the neurovascular bundle surrounding prostate, makes they should be preserved sparing the pseudocapsule by a gentle fibroid removal, possibly by minimally invasive surgical technique, as laparoscopy, with all the reported advantages on patients [26]. For this reason, during myomectomy, the fibroid pseudocapsule needs to be always gently protected, avoiding destructive proceedings such as large diathermocoagulation at high electrical wattage (more than 30 W), who alters these neurotransmitters distribution in myoma pseudocapsule [52].

In urological surgery, the goal is to preserve the neurovascular bundle, which is located outside the prostatic capsule, to prevent erectile dysfunction (impotency) and urinary incontinence. Nerve sparing techniques for anatomic radical prostatectomy developed in the recent years have helped to reduce complications related to injuries of neurovascular bundle. A commonly used approach for neurovascular bundle preservation involves early incision of the lateral prostatic fascia, partial mobilization of the neurovascular bundle from the apical third of the gland, and then urethral transection and subsequent elevation of the apex of the prostate, generally with a Foley catheter as a tractor, to ensure the lateralization of the neurovascular bundle and posterior dissection of the prostate. Early release of the neurovascular bundle from the apex of the prostate before beginning the posterior dissection reduces the time to recovery and improves function [69].

So as the neurovascular bundle surrounding prostate is rich of neurotransmitters and it need to be always preserved during radical prostatectomy to maintain urinary and sexual function, as myoma pseudocapsule is a neurovascular bundle rich of neurofibers and neuropeptides, and it need to be always preserved during myomectomy to allow a better healing of the uterine scar, extremely important for uterine musculature successive reproductive functionality.

The clinical rationale of intracapsular myomectomy can be applied to all myomectomies, and it is relevant, since a proper laparoscopic myomectomy dramatically improves fertility, reduces blood loss, shortens hospital stay, and minimizes therapeutic antibiotic administration [14, 70].

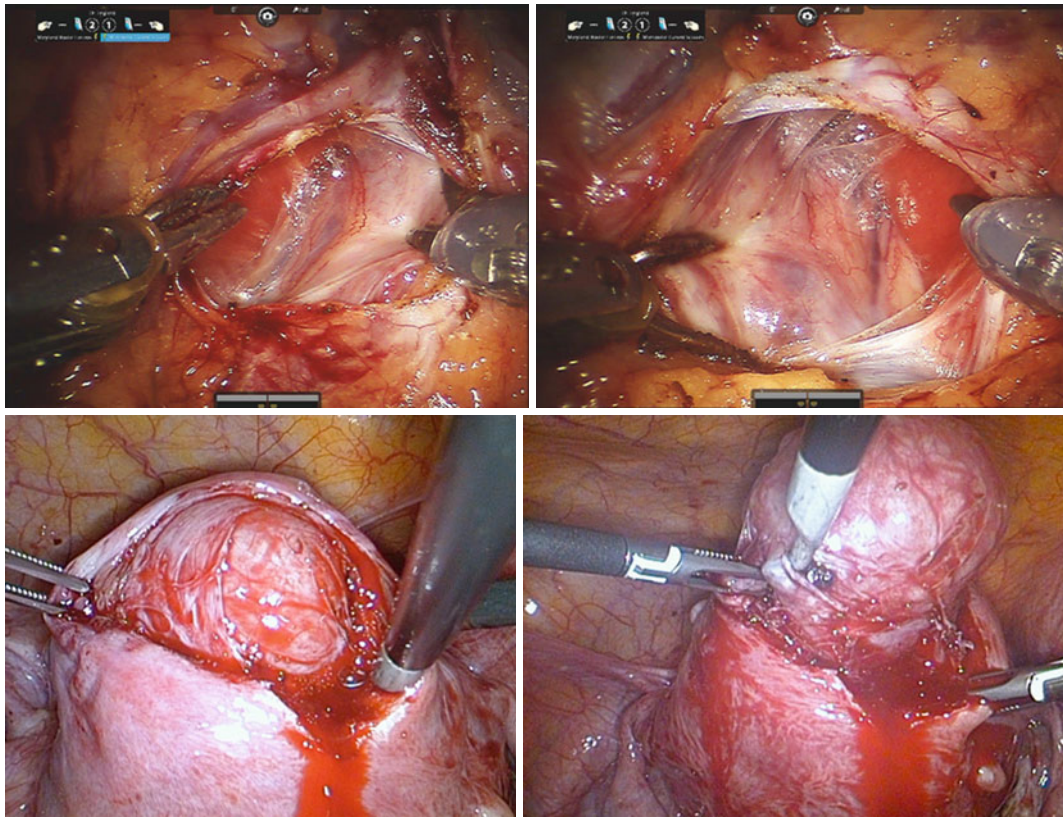

Fig. 6.11 On the *upper side*, the two images show the endoscopic incision of the prostatic capsule during a robotic prostatectomy by Da Vinci Robot, shoving prostatic vein and neurovascular bundle surrounding prostate. On the *underside*, the two images show the endoscopic incision of the uterine serosa, the fibroid exposure surrounded by pseudocapsule during a laparoscopic myomectomy and fibroid enucleation by cutting of the fibrovascular pseudocapsule branches

The Rationale of Intracapsular Myomectomy: Pro and Cons

The general myomectomy dogma is that "each surgical fibroid enucleating needs to be gently performed to enhance a correct healing process of the uterine musculature and to facilitate successively the correct uterine musculature anatomical-functional restoring".

During myomectomy, as reported by literature [71], the fibroid pseudocapsule neurovascular bundle needs to be always protected, avoiding destructive surgical proceedings such as extensive and high wattage diathermocoagulation (>30 W) or excessive tissue manipulating or trauma. This method of myomectomy maximally respects the fibroid pseudocapsule neurovascular bundle, rich of neurofibers involved in the correct successive scar healing. The iatrogenic myoma pseudocapsule damage should therefore alter the successive neurotransmitters' function in myometrial repair, with negative effect on uterine healing. Thus, the surgical sequels of an uncorrected myomectomy with pseudocapsule damaging should be: a reduction in neurofibers' presence at hysterotomic site, a deterioration of uterine musculature healing, and a deficit either of myometrial neurotransmission or of muscular impulse and contractility, with final reduced uterine musculature functionality.

This argumentation is even more important for the different localization of fibroids, because the thickness of the pseudocapsule is changed depending on the location of the fibroid in the myometrium.

This structure was analyzed in its thickness [72] by a study involving ultrasound and histology data matching on: subserosal fibroids (SSF); intramural fibroids (IMF) and fibroids near the endometrial cavity (FEC). FEC's pseudocapsules were considerably thicker than those of IMF and SSF measured by US and histology (P = 0.001). A clear cut-off existed between FEC pseudocapsule thickness and all other pseudocapsules, with significant differences observed at 2 mm (P = 0.001). Similarity between histological and US measurements was observed only with IMF pseudocapsules, whereas FEC or SSF showed significant differences. The pseudocapsule of fibroids is considerably thicker near the endometrial cavity when compared those of both intramural and subserosal fibroids. Since fibroids closest to the endometrial cavity are the most involved in fertility and infertility [73, 74] and fibroid pseudocapsule is considerably thicker near the endometrial cavity, it is possible to hypothesize an involvement of fibroid pseudocapsule especially near on endometrium, since pseudocapsule contains many neuropeptides and neurotransmitters that are physiologically active.

Despite these evidences, there are many topics to discuss about myomectomy commonly worldwide performed.

On of the first question concerns the current use of techniques that minimize the blood loss and to occlude uterine blood supply during myomectomy, as Tourniquet methods [75, 76], uterine artery embolization [77] or ligation [78], intrauterine injection of ischemic solutions [79, 80] or gonadotrophin-releasing hormone (GnRH) analogues [81, 82].

All these methods try to reduce blood flow into the pseudocapsule, by mechanical compression (the tourniquet methods), vascular occlusion or pharmacological blood flow decreasing.

In authors' opinion, the main problem they have is that their use could mask the musculature vascularization for vessel collapsing, making difficult the selective and gentle pseudocapsule vessel hemostasis during myomectomy and favoring successive intra-myometrial hematomas, detecting by ultrasounds [30, 83], with impairment of the muscular healing at hysterotomic site.

On the contrary, during surgery, the fibroid pseudocapsule neurovascular bundle needs to be well exposed by endoscopic magnification [52, 59], and carefully protected avoiding destructive proceedings, such as large diathermocoagulation at high wattage favoring an incorrect restoring of uterine musculature [71].

Analyzing then literature on ischemic solutions to inject into myometrium, studies showed that vasopressin decreased blood loss at time of myomectomy by laparotomy compared with placebo or a tourniquet. On the other hand, other studies founded no difference between the use of vasopressin or a tourniquet at myomectomy performed by laparotomy [80, 84]. In clinical practice, probably either technique will decrease blood loss compared with no intervention, so as the greater magnification afforded by the laparoscope may allow for more-precise treatment of blood vessels. In addition, the pneumoperitoneum by CO_2 associated with laparoscopy may tamponade small vessels and, cumulatively, result in less blood loss [52, 59].

Vasopressin injection has been unfortunately reported to cause pulmonary edema and, with intravenous injection, even death, while loop ligation may ultimately compromise uterine function and may reduce fertility or increase complications during pregnancy [81].

Moreover, the exclusion of preoperative GnRH-analogue treatment is due to reported increased risk of fibroid recurrence, a possible delay in the diagnosis of leiomyosarcoma, a risk of massive hemorrhage from degeneration [85], and, primarily, to avoid distortion of the myoma pseudocapsule. The GnRH-analogue treatment decreases the size of the myoma causing confluent nodular hyaline degeneration and hydropic degeneration necrosis, masking moreover the correct cleavage plan between myoma and pseudocapsule and making ever difficult the myoma hooking [82, 86]. For this reason, in authors' opinion, the use of ischemic solutions and GnRH-analogues before surgery is useless and even harmful in some cases.

It is likely that the suturing technique, in authors' opinion, is of secondary importance when an intracapsular myomectomy is well performed. The problem of stitches has never been

well approached in myomectomy for the lack of well stated scientific rationale.

As already showed, the myoma pseudocapsule is a fibro neurovascular structure probably created by uterus to cope with the development and growing of fibroid; when surgeon gently remove myoma through pseudocapsule, he/her preserves the muscle surrounding myoma, returning to normality as an healthy uterine tissue. The same thing happens in the lower uterine segment during pregnancy: after delivery, it disappears. For these reasons, the hysterorraphy after intracapsular myomectomy, in authors' opinion, need to be closed by simply introflecting muscle edges, approaching in one or two layers. The various described sutures in several layers have no reason to be used, since more foreign body suture materials produces inflammatory reactions, based on submesothelial fibrosis, strengthened by regenerative mesothelial hyperplasia [87].

In such way, after intracapsular fibroid removal, which spares neurovascular fibers and neuropeptides, the uterine muscle is healthy and not traumatized, ready for a proper healing. And, if the myoma is enucleated entirely through the fibrovascular capsule opening, using blunt or sharp dissection on the surrounding myometrium, with a gentle selective low energy hemostasis on pseudocapsule' vessels, the myometrial bed collapses without excessive bleeding once the myoma is removed. This is the rationale for which is not so necessary to give too much importance to the technique of suturing, while the opposite is the technique itself that preserves myometrial integrity and allows the restoration of uterine musculature, with magnification of pseudocapsule neurovascular bundle using laparoscopy or robotic-assisted surgery, as a sort of endoscopic tailored micro-surgery.

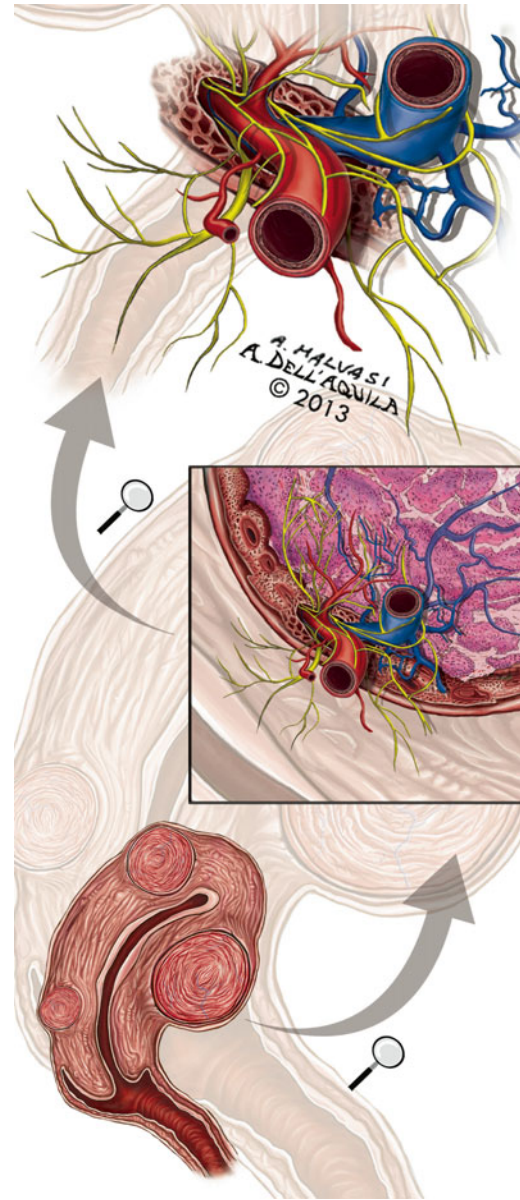

Fig. 6.12 Myoma pseudocapsule is a dense fibroneurovascular pseudocapsule surrounding fibroid (at the *centre* of figure), rich of neurotrasmitters and growth factors (on the *top*), with a proper angiogenic profile that covers all uterine myomas (*bottom image*)

Conclusions

Uterine fibroid is a monoclonal growth of fibrovascular cells that arise from the myometrium. The fibroid deforms the surrounding myometrium as it grows, giving rise to a dense fibroneurovascular pseudocapsule, rich of neurotrasmitters and growth factors, with a proper angiogenic profile (Fig. 6.12). In recent years, new advancements in endoscopic surgery, including the use of laparoscopic or robotic surgery, have been considered as the true alternative to laparotomy in fibroids removal with numerous advantages, such as short hospitalization, decreased need for postoperative anal-

gesia, less intraoperative blood loss, and good outcomes in subsequent pregnancy [6–8]. Last evidences on the presence of dedicate angiogenesis, neurofibers and neuropeptides in pseudocapsule suggested to preserve as much as possible such structure, during myomectomy. Pseudocapsule sparing during myomectomy should preserve myometrium integrity peripheral to fibroid site, enhancing myometrial healing after myomectomy. Moreover, intracapsular endoscopic myomectomy should favor reproductive outcomes and normal labor and delivery, for less bleeding [59], better neurovascular bundle sparing [71], and post-operative adhesions reduction [11]. So the mix of intracapsular myomectomy and pseudocapsule-sparing by endoscopic "microsurgical" magnification, can be reproduced in all myomectomies, as a safe and feasible minimally invasive technique [52].

Disclosure of Interest Authors certify that there is no actual or potential conflict of interest in relation to this article and they reveal any financial interests or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated – including pertinent commercial or other sources of funding for the individual author(s) or for the associated department(s) or organization(s), personal relationships, or direct academic competition.

References

1. Bulun SE. Uterine fibroids. N Engl J Med. 2013; 369(14):1344–55.
2. Evans P, Brunsell S. Uterine fibroid tumors: diagnosis and treatment. Am Fam Physician. 2007;75(10):1503–8.
3. Somigliana E, Vercellini P, Daguati R, Pasin R, De Giorgi O, Crosignani PG. Fibroids and female reproduction: a critical analysis of the evidence. Hum Reprod Update. 2007;13(5):465–76.
4. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol. 1990;94(4):435–8.
5. Catherino WH, Parrott E, Segars J. Proceedings from the National Institute of Child Health and Human Development conference on the Uterine Fibroid Research Update Workshop. Fertil Steril. 2011;95: 9–12.
6. Khan AT, Shehmar M, Gupta JK. Uterine fibroids: current perspectives. Int J Womens Health. 2014;6: 95–114.
7. Falcone T, Parker WH. Surgical management of leiomyomas for fertility or uterine preservation. Obstet Gynecol. 2013;121(4):856–68. doi:10.1097/AOG.0b013e3182888478.
8. Lethaby A, Vollenhoven B. Fibroids (uterine myomatosis, leiomyomas). Clin Evid. 2011;2011. pii: 0814.
9. Stovall DW. Alternatives to hysterectomy: focus on global endometrial ablation, uterine fibroid embolization, and magnetic resonance-guided focused ultrasound. Menopause. 2011;18(4):443–50.
10. Tinelli A, Malvasi A, Rahimi S, Negro R, Cavallotti C, Vergara D, Vittori G, Mettler L. Myoma pseudocapsule: a distinct endocrino-anatomical entity in gynecological surgery. Gynecol Endocrinol. 2009;25(10): 661–7.
11. Tinelli A, Malvasi A, Guido M, Tsin DA, Hudelist G, Hurst B, Stark M, Mettler L. Adhesion formation after intracapsular myomectomy with or without adhesion barrier. Fertil Steril. 2011;95(5):1780–5.
12. Tinelli A, Malvasi A, Cavallotti C, Dell'Edera D, Tsin DA, Stark M, Mettler L. The management of fibroids based on immunohistochemical studies of their pseudocapsules. Expert Opin Ther Targets. 2011;15(11):1241–7.
13. Pasetto N, Baschieri L, Giacomello F, Ticconi C. Patologia benigna dell'utero. In: Candiani GB, Danesino V, Gastaldi C, editors. La clinica ostetrica e ginecologica. Milan: Masson Editore; 1992. p. 1242–56.
14. Hurst BS. Uterine fibroids, chapter 10. In: Stadtmauer LA, Tur-Kaspa I, editors. Ultrasound imaging in reproductive medicine. New York: Springer; 2014. p. 117–31.
15. Faulkner RL. The blood vessels of the myomatous uteri. Am J Obstet Gynecol. 1944;47:185–97.
16. Farrer-Brown G, Beilby JOW, Tarbit MH. The vascular patterns in myomatous uteri. J Obstet Gynaecol. 1970;77:967–75.
17. Awataguchi K. Studies on the angioarchitecture of uterine myoma. Nippon Ika Daigaku Zasshi. 1982;49: 225–32.
18. Casey R, Rogers PA, Vollenhoven BJ. An immunohistochemical analysis of fibroid vasculature. Hum Reprod. 2000;15(7):1469–75.
19. Campo S, Garcea N. Laparoscopic myomectomy in premenopausal women with and without preoperative treatment using gonadotrophin-releasing hormone analogues. Hum Reprod. 1999;14:44–8.
20. Lethaby A, Vollenhoven B, Sowter M. Pre-operative Gn-RH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database Syst Rev. 2001;(2):CD000547.
21. Pinkerton JV. Pharmacological therapy for abnormal uterine bleeding. Menopause. 2011;18(4):459–67.
22. Walocha JA, Litwin JA, Miodonski A. Vascular system of intramural leiomyomata revealed by corrosion casting and scanning electron microscopy. Hum Reprod. 2003;18:1088–93.
23. Forssman L. Blood flow in myomatous uteri as measured by intraarterial 133-Xenon. Acta Obstet Gynecol Scand. 1976;55:21–4.

24. Malvasi A, Cavallotti C, Morroni M, Lorenzi T, Dell'Edera D, Nicolardi G, Tinelli A. Uterine fibroid pseudocapsule studied by transmission electron microscopy. Eur J Obstet Gynecol Reprod Biol. 2012;162(2):187–91.
25. Wei JJ, Zhang XM, Chiriboga L, Yee H, Perle MA, Mittal K. Spatial differences in biologic activity of large uterine leiomyomata. Fertil Steril. 2006;85:179–87.
26. Mettler L, Tinelli A, Hurst BS, Teigland CM, Sammur W, Dell'Edera D, Negro R, Gustapane S, Malvasi A. Neurovascular bundle in fibroid pseudocapsule and its neuroendocrinologic implications. Expert Rev Endocrinol Metab. 2011;6(5):715–22.
27. Malvasi A, Tinelli A, Cavallotti C, Morroni M, Tsin DA, Nezhat C, et al. Distribution of substance P (SP) and vasoactive intestinal peptide (VIP) in pseudocapsules of uterine fibroids. Peptides. 2011;32:327–32.
28. Malvasi A, Cavallotti C, Nicolardi G, Pellegrino M, Dell'edera D, Vergara D, et al. NT, NPY and PGP 9.5 presence in myometrium and in fibroid pseudocapsule and their possible impact on muscular physiology. Gynecol Endocrinol. 2013;29:177–81.
29. Malvasi A, Cavallotti C, Nicolardi G, Pellegrino M, Vergara D, Greco M, et al. The opioid neuropeptides in uterine fibroid pseudocapsules: a putative association with cervical integrity in human reproduction. Gynecol Endocrinol. 2013;29:982–8.
30. Tinelli A, Hurst BS, Mettler L, Tsin DA, Pellegrino M, Nicolardi G, et al. Ultrasound evaluation of uterine healing after laparoscopic intracapsular myomectomy: an observational study. Hum Reprod. 2012;27:2664–70.
31. Delgado AV, McManus AT, Chambers JP. Exogenous administration of Substance P enhances wound healing in a novel skin-injury model. Exp Biol Med (Maywood). 2005;230:271–80.
32. Jiang MH, Chung E, Chi GF, Ahn W, Lim JE, Hong HS, et al. Substance P induces M2-type macrophages after spinal cord injury. Neuroreport. 2012;23:786–92.
33. Malvasi A, Tinelli A, Cavallotti C, Bettocchi S, Di Renzo GC, Stark M. Substance P (SP) and vasoactive intestinal polypeptide (VIP) in the lower uterine segment in first and repeated cesarean sections. Peptides. 2010;31:2052–9.
34. Collins JJ, Usip S, McCarson KE, Papka RE. Sensory nerves and neuropeptides in uterine cervical ripening. Peptides. 2002;23:167–83.
35. Tingaker BK, Ekman-Ordeberg G, Facer P, Irestedt L, Anand P. Influence of pregnancy and labor on the occurrence of nerve fibers expressing the capsaicin receptor TRPV1 in human corpus and cervix uteri. Reprod Biol Endocrinol. 2008;6:8.
36. Tingaker BK, Ekman-Ordeberg G, Forsgren S. Presence of sensory nerve corpuscles in the human corpus and cervix uteri during pregnancy and labor as revealed by immunohistochemistry. Reprod Biol Endocrinol. 2006;4:45.
37. Cormio L, Gesualdo L, Maiorano E, Bettocchi C, Palumbo F, Traficante A, et al. Vasoactive intestinal polypeptide (VIP) is not an androgen-dependent neuromediator of penile erection. Int J Impot Res. 2005;17:23–6.
38. Rodríguez R, Pozuelo JM, Martín R, Arriazu R, Santamaria L. Stereological quantification of nerve fibers immunoreactive to PGP 9.5, NPY, and VIP in rat prostate during postnatal development. J Androl. 2005;26:197–204.
39. Arms L, Vizzard MA. Neuropeptides in lower urinary tract function. Handb Exp Pharmacol. 2011;202:395–423.
40. Merrill L, Girard B, Arms L, Guertin P, Vizzard MA. Neuropeptide/receptor expression and plasticity in micturition pathways. Curr Pharm Des. 2013;19:4411–22.
41. Yucel S, Erdogru T, Baykara M. Recent neuroanatomical studies on the neurovascular bundle of the prostate and cavernosal nerves: clinical reflections on radical prostatectomy. Asian J Androl. 2005;7(4):339–49.
42. Takenaka A, Murakami G, Soga H, Han SH, Arai Y, Fujisawa M. Anatomical analysis of the neurovascular bundle supplying penile cavernous tissue to ensure a reliable nerve graft after radical prostatectomy. J Urol. 2004;172(3):1032–5.
43. Costello AJ, Brooks M, Cole OJ. Anatomical studies of the neurovascular bundle and cavernosal nerves. BJU Int. 2004;94(7):1071–6.
44. Walsh PC. The discovery of the cavernous nerves and development of nerve sparing radical retropubic prostatectomy. J Urol. 2007;177(5):1632–5.
45. Hernandez DJ, Epstein JI, Trock BJ, Tsuzuki T, Carter HB, Walsh PC. Radical retropubic prostatectomy. How often do experienced surgeons have positive surgical margins when there is extraprostatic extension in the region of the neurovascular bundle? J Urol. 2005;173(2):446–9.
46. Shah SJ, Goyal V, Sachar R, Nath AK, Jain N, Kapadia K. Seminal vesicle sparing laparoscopic radical prostatectomy using a low-energy source: better continence and potency. Indian J Urol. 2009;25(2):199–202.
47. Han M, Kim C, Mozer P, Schäfer F, Badaan S, Vigaru B, Tseng K, Petrisor D, Trock B, Stoianovici D. Tandem-robot assisted laparoscopic radical prostatectomy to improve the neurovascular bundle visualization: a feasibility study. Urology. 2011;77(2):502–6.
48. Walz J, Burnett AL, Costello AJ, Eastham JA, Graefen M, Guillonneau B, Menon M, Montorsi F, Myers RP, Rocco B, Villers A. A critical analysis of the current knowledge of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. Eur Urol. 2010;57(2):179–92.
49. Lee SE, Hong SK, Han JH, Han BK, Yu JH, Jeong SJ, Byun SS, Lee HJ. Significance of neurovascular bundle formation observed on preoperative magnetic resonance imaging regarding postoperative erectile function after nerve-sparing radical retropubic prostatectomy. Urology. 2007;69(3):510–4.

50. Ong AM, Su LM, Varkarakis I, Inagaki T, Link RE, Bhayani SB, Patriciu A, Crain B, Walsh PC. Nerve sparing radical prostatectomy: effects of hemostatic energy sources on the recovery of cavernous nerve function in a canine model. J Urol. 2004;172(4 Pt 1):1318–22.
51. Ukimura O, Gill IS. Real-time transrectal ultrasound guidance during nerve sparing laparoscopic radical prostatectomy: pictorial essay. J Urol. 2006;175(4): 1311–9.
52. Tinelli A, Malvasi A, Hudelist G, Cavallotti C, Tsin DA, Schollmeyer T, Bojahr B, Mettler L. Laparoscopic intracapsular myomectomy: comparison of single versus multiple fibroids removal. An institutional experience. J Laparoendosc Adv Surg Tech A. 2010;20(8):705–11.
53. Tinelli A, Hurst BS, Hudelist G, Tsin DA, Stark M, Mettler L, Guido M, Malvasi A. Laparoscopic myomectomy focusing on the myoma pseudocapsule: technical and outcome reports. Hum Reprod. 2012;27(2):427–35.
54. Ito F, Kawamura N, Ichimura T, Tsujimura A, Ishiko O, Ogita S. Ultrastructural comparison of uterine leiomyoma cells from the same myoma nodule before and after gonadotropin-releasing hormone agonist treatment. Fertil Steril. 2001;75: l25–130.
55. Dapunt O. Studies on the structure of the myoma capsule. Arch Gynecol. 1965;202:492–4.
56. Fox H, Buckley CH. Benign neoplasms of the female genital tract. In: Pathology for gynaecologists, vol. 8. London: Arnold Ed; 1982. p. 91–7.
57. Vizza E, Motta PM. The skeleton fibrous and muscolar of the uterus. In: Atti LXXVII Congresso SIGO. Rome: CIC Int Ed; 2001. p. 47–9.
58. Hsu WC, Hwang JS, Chang WC, Huang SC, Sheu BC, Torng PL. Prediction of operation time for laparoscopic myomectomy by ultrasound measurements. Surg Endosc. 2007;21(9):1600–6.
59. Tinelli A, Mettler L, Malvasi A, Hurst B, Catherino W, Mynbaev OA, Guido M, Alkatout I, Schollmeyer T. Impact of surgical approach on blood loss during intracapsular myomectomy. Minim Invasive Ther Allied Technol. 2014;23(2):87–95.
60. Di Tommaso S, Massari S, Malvasi A, Bozzetti MP, Tinelli A. Gene expression analysis reveals an angiogenic profile in uterine leiomyoma pseudocapsule. Mol Hum Reprod. 2013;19(6):380–7.
61. Stewart EA, Nowak RA. Leiomyoma-related bleeding: a classic hypothesis updated for the molecular era. Hum Reprod Update. 1996;2(4):295–306.
62. Hanna KR, Katz AJ. An update on wound healing and the nervous system. Ann Plast Surg. 2011;67(1): 49–52.
63. Henderson J, Terenghi G, Ferguson MW. The reinnervation and revascularisation pattern of scarless murine fetal wounds. J Anat. 2011;218(6):660–7.
64. Gouin JP, Carter CS, Pournajafi-Nazarloo H, Glaser R, Malarkey WB, Loving TJ, Stowell J, Kiecolt-Glaser JK. Marital behavior, oxytocin, vasopressin, and wound healing. Psychoneuroendocrinology. 2010; 35(7):1082–90.
65. Malvasi A, Tinelli A, Rahimi S, D'Agnese G, Rotoni C, Dell'edera D, Tsin DA, Cavallotti C. A three-dimensional morphological reconstruction of uterine leiomyoma pseudocapsule vasculature by the Allen-Cahn mathematical model. Biomed Pharmacother. 2011;65(5):359–63.
66. Vikhareva Osser O, Valentin L. Risk factors for incomplete healing of the uterine incision after caesarean section. BJOG. 2010;117(9):1119–26.
67. Kubinova K, Mara M, Horak P, Kuzel D, Dohnalova A. Reproduction after myomectomy: comparison of patients with and without second-look laparoscopy. Minim Invasive Ther Allied Technol. 2012;21(2):118–24.
68. Quinn MJ, Kirk N. Differences in uterine innervation at hysterectomy. Am J Obstet Gynecol. 2002;187(6): 1515–20.
69. Masterson TA, Serio AM, Mulhall JP, Vickers AJ, Eastham JA. Modified technique for neurovascular bundle preservation during radical prostatectomy: association between technique and recovery of erectile function. BJU Int. 2008;101(10):1217–22.
70. Hurst BS, Matthews ML, Marshburn PB. Laparoscopic myomectomy for symptomatic uterine myomas. Fertil Steril. 2005;83(1):1–23.
71. Tinelli A, Malvasi A, Hurst BS, Tsin DA, Davila F, Dominguez G, Dell'Edera D, Cavallotti C, Negro R, Gustapane S, Teigland CM, Mettler L. Surgical management of neurovascular bundle in uterine fibroids pseudocapsule. JSLS. 2012;16:119–29.
72. Tinelli A, Mynbaev OA, Mettler L, Hurst BS, Pellegrino M, Nicolardi G, Kosmas I, Malvasi A. A combined ultrasound and histologic approach for analysis of uterine fibroid pseudocapsule thickness. Reprod Sci. 2014;21:1177–86. pii:1933719114537719.
73. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril. 2009;91(4):1215–23.
74. Shavell VI, Thakur M, Sawant A, Kruger ML, Jones TB, Singh M, Puscheck EE, Diamond MP. Adverse obstetric outcomes associated with sonographically identified large uterine fibroids. Fertil Steril. 2012;97(1):107–10.
75. Ikechebelu JI, Ezeama CO, Obiechina NJ. The use of torniquet to reduce blood loss at myomectomy. Niger J Clin Pract. 2010;13(2):154–8.
76. Al-Shabibi N, Chapman L, Madari S, Papadimitriou A, Papalampros P, Magos A. Prospective randomised trial comparing gonadotrophin-releasing hormone analogues with triple tourniquets at open myomectomy. BJOG. 2009;116(5):681–7.
77. Firouznia K, Ghanaati H, Jalali AH, Shakiba M. Uterine artery embolization for treatment of symptomatic fibroids: a review of the evidence. Iran Red Crescent Med J. 2013;15(12):e16699.
78. Chang WC, Chou LY, Chang DY, Huang PS, Huang SC, Chen SY, Sheu BC. Simultaneous laparoscopic uterine artery ligation and laparoscopic myo-

mectomy for symptomatic uterine myomas with and without in situ morcellation. Hum Reprod. 2011;26(7): 1735–40.
79. Riess ML, Ulrichs JG, Pagel PS, Woehlck HJ. Severe vasospasm mimics hypotension after high-dose intrauterine vasopressin. Anesth Analg. 2011;113(5): 1103–5.
80. Frishman GN, Jurema MW. Myomas and myomectomy. J Minim Invasive Gynecol. 2005;12:443–56.
81. Chen I, Motan T, Kiddoo D. Gonadotropin-releasing hormone agonist in laparoscopic myomectomy: systematic review and meta-analysis of randomized controlled trials. J Minim Invasive Gynecol. 2011;18(3): 303–9.
82. Al-Talib A. Factors contributing to failure of laparoscopic myomectomy. Surg Technol Int. 2013;23: 149–51.
83. Chang WC, Chang DY, Huang SC, Shih JC, Hsu WC, Chen SY, Sheu BC. Use of three-dimensional ultrasonography in the evaluation of uterine perfusion and healing after laparoscopic myomectomy. Fertil Steril. 2009;92(3):1110–5.
84. Frederick S, Frederick J, Fletcher H, Reid M, Hardie M, Gardner W. A trial comparing the use of rectal misoprostol plus perivascular vasopressin with perivascular vasopressin alone to decrease myometrial bleeding at the time of abdominal myomectomy. Fertil Steril. 2013;100(4):1044–9.
85. Sankaran S, Manyonda IT. Medical management of fibroids. Best Pract Res Clin Obstet Gynaecol. 2008;22(4):655–76.
86. De Falco M, Staibano S, Mascolo M, Mignogna C, Improda L, Ciociola F, Carbone IF, Di Lieto A. Leiomyoma pseudocapsule after pre-surgical treatment with gonadotropin-releasing hormone agonists: relationship between clinical features and immunohistochemical changes. Eur J Obstet Gynecol Reprod Biol. 2009;144(1):44–7.
87. Malvasi A, Tinelli A, Farine D, Rahimi S, Cavallotti C, Vergara D, Martignago R, Stark M. Effects of visceral peritoneal closure on scar formation at cesarean delivery. Int J Gynaecol Obstet. 2009;105(2):131–5.

Adenomyosis and Adenomyomata

7

George A. Pistofidis

Introduction

Uterine adenomyosis has been, and remains, a diagnostic and operative challenge. Most cases of diffused adenomyosis are correctly diagnosed by MRI or vaginal ultrasonography. However, some sub-types of adenomyotic lesions can disguise themselves or coincide with a diversity of clinical entities causing symptoms that don't necessarily direct you to the ideal therapeutic decision. Generally, all these lesions have, until now, been grouped under the title of focal adenomyosis.

For over 15 years, all cases managed in our centre were carefully recorded and analysed. Inclusion parameters were: age of the patient, symptomatology, ultrasound imaging, uterine topography of the lesion, surgical outcome and histology report. All patients have been followed for at least 2 years and the majority for over five. In cases where surgery was not performed, lesions and symptomatology were monitored to see the natural progression of the disease. Four expressions of uterine adenomyotic lesions were repeatedly observed: diffuse, nodular, sclerotic and cystic. Most types apart from diffused adenomyosis were managed successfully by laparoscopy.

G.A. Pistofidis MBBS, FROG
Director of Gynaecological Endoscopic Surgery,
Levkos Stavros Clinic, Athens, Greece
e-mail: george@pistofidis.eu

Historical Background

The term 'adenomyoma' was used for the first time in 1860 by the Austrian pathologist Carl Freiherr von Rokitansky [1]. He found endometrial glands in the myometrium and described this finding as 'cystosarcoma adenoids uterinum.' More than half a century elapsed before Thomas Stephen Cullen presented in 1920 a detailed description of what we intend today as uterine adenomyosis [2]. He clearly described the mechanism of mucosal invasion of the underlying myometrium and further separated the adenomyotic lesions into diffused and focal. However, Frankl in 1925, 2 years before Sampson created the word 'endometriosis' and distinguished the two conditions, clearly described the anatomical picture and coined the term 'adenomyosis uteri'. He justified the term "adenomyosis" so that he could distinguish this condition from inflammatory lesions such as adenometritis, adenomyometritis or adenomyositis [3].

Histological Definition

The definition of adenomyosis, as it stands today, was defined by C Bird et al. in 1972. He proposed that adenomyosis results due to "benign invasion of endometrium in the myometrium, producing a diffused enlarged uterus, which microscopically exhibits ectopic, non–neoplastic, endometrial glands and stroma surrounded by hypertrophic and hyperplastic myometrium" [4].

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Etiology of Adenomyosis

Initially, the theories proposed to explain formation of adenomyosis, were the Wolffian body theory by F. von Recklinghausen in 1893 [5], the mucosal invading theory by T Cullen in 1896 [6], the Mullerian duct hypothesis by R Kossmann in 1897 [7] and the serosal extending theory by NS Ivanoff 1898 [8]. Finally, Meyer proposed a combined hypothesis where the surface epithelium, serosa, or mucosa would invaginate into the underlying stroma, a process that would promote local inflammation resulting in the formation of adenomyotic nodules [9].

The precise aetiology and developmental events leading to adenomyosis are even today undetermined. Clinical studies hypothesize that adenomyosis results when endometrial glands invade the myometrial layer ([4], Ferenczy 1998). In addition to endometrial glands and stroma invasion, Bird et al. suggested that the diagnosis of adenomyosis required the identification of a smooth-muscle hyperplasia reaction [10]. It is thought that disruptions of the endometrial-myometrial border allows for a reactive hyperplasia of the endometrial basalis layer and its extension into myometrium [11]. To date, the main histopathologic feature of adenomyosis is the existence of myometrial hypertrophy around foci of adenomyosis and the distance between the endomyometrial junction and the closest adenomyotic foci which should comprise at least 25 % of the total thickness of the myometrium [12].

Five further theories were recently advanced to explain the formation of adenomyosis:

1. **Traumatic**: adenomyosis ensues as a consequence of invagination of the basalis endometrium into the myometrium due to weakened myometrium from local trauma from previous surgery [13].
2. **Immunological**: endometrial invagination occurs due to an aberrant immune phenomenon of the affected tissue. Evidence to support this hypothesis derives from immunochemistry studies that show that increased numbers of macrophages, activate T and B cells to produce antibodies and cytokines which in turn can disrupt the endometrial junctional zone [14].
3. **Hormonal**: studies have shown that adenomyotic tissue contains higher estrogen receptors than eutopic endometrium. This locally could promote invagination of the endometrium and propagation of adenomyosis. In addition, adenomyotic tissue contains aromatase enzymes that locally produce estrogens adding to further growth of abnormal endometriotic glands [15].
4. **Metaplastic**: de novo formation of adenomyotic foci from Mullerian remnants. This theory supports the formation of nodular adenomyosis of the uterus which in turns shares common etiologic pathways with deep endometriotic nodules of the rectovaginal septum. Atopic endometrium found in adenomyosis does not seem to share similar biological characteristics with the eutopic endometrium. Additionally, atopic endometrium did not respond to hormonal changes in the same way as eutopic endometrium, secretory changes were rare and finally did not demonstrate cyclic properties of the induction of apoptosis regulatory proteins such as bel-2 expression [16]. These findings suggest that some forms of adenomyosis do not originate from eutopic endometrium.
5. **Stem cell theory:** this theory is supported by research demonstrating that endometrial regeneration can be driven by bone marrow-derived stem cells. Data exist to suggest that bone marrow – derived stem cells can contribute to repopulation of new endometrium. Thus, such stem cells could also find their way and grow within the uterine myometrium inducing local proliferation of uterine glands and stroma [17].

Diagnostic Methods and the Uterine Junctional Zone

Our understanding of the physiology and pathophysiology of the uterus has changed since the advent of magnetic imaging techniques (MRI)

some 25 years ago. With this method a new functional uterine zone between the endometrium and myometrium has been identified: the Junctional Zone (JZ) [18]. The JZ possesses a specific feature that separates it from other similar junctions of the human body. It lacks a recognizable protective layer thus forcing the endometrial glands into direct contact with the myometrium. The JZ changes in appearance and thickness during the menstrual cycle, reaching maximum growth between days eight and sixteen. Abdominal sonography has also shown distinct peristaltic activity that seems to originate from the JZ. The direction and intensity of peristalsis increase in cervical-fundal direction during the follicular phase and ovulation, whilst reduced intensity and movement in the opposite direction, during the luteal phase [19].

In healthy young women the thickness of JZ measures of 5 mm or less whilst it is clearly thickened in the presence of adenomyosis [20]. Gordts et al. recently proposed a classification system for adenomyosis: simple JZ hyperplasia (zone thickness >8 mm but <12 mm on T2-weighted images, in women less than 33 years), partial or diffuse adenomyosis (thickness >12 mm; high signal intensity myometrial foci; involvement of the outer myometrium: <1/3, <2/3, >2/3), adenomyoma (myometrial mass with indistinct margins of primarily low-signal intensity on all MRI sequences) [21]. However, this classification remains to be validated.

Some workers believe that MRI offers superior diagnostic capacity than vaginal sonography (VS), having equal sensitivity (MRI 0.70 vs. VS 0.68) but a higher specificity (MRI 0.86 vs. VS 0.65 [21]). Exacustos et al. have shown that the presence of myometrial inclusion cysts represent the most specific 2D-VS feature for correct diagnosis of adenomyosis with a specificity of 98 % and sensitivity of 78 % [22].

Terms to describe adenomyosis during examination with VS include: heterogeneous myometrial area, globular asymmetric uterus, irregular cystic spaces or myometrial lacunae, myometrial linear striations, poor definition of myometrial junction, myometrial anterior-posterior asymmetry, thickening of anterior-posterior wall with increased or decreased echogenicity, irregularly shaped mass with lack of pseudo-capsule. Expressions used to define adenomyosis by MRI include: diffuse or local widening of JZs, JZ wider than 12 mm, subjective thickening of JZ localized or diffuse, ill-defined low intensity lesion, TZ thickness of 15 mm, uterine enlargement with small hypo-intense myometrial spots.

Symptomatology and Types of Adenomyosis

Although a large proportion of patients with adenomyosis are asymptomatic, adenomyosis is known to be associated with menorrhagia, dysmenorrhea and subfertility [23]. In our series, 63 % of the patients presented with menorrhagia, 40 % with dysmenorrhea and only 7 % with subfertility. Although in some series adenomyosis and infertility are related [24], our centre, being a tertiary surgical reference facility, was less likely to treat patients with infertility as their presenting complaint.

In the literature, adenomyosis remains a neglected condition despite being a prominent uterine pathology, 20–30 % of all women undergoing hysterectomy are due to adenomyosis [25]. On PubMed, out of 31,626 papers referring to endometriosis, fibroids and adenomyosis, written between 1905 and 2013, only 6.7 % were linked to adenomyosis, whilst only 3.6 % out of 4,476 papers associated with the same conditions but treated by laparoscopy, were adenomyosis papers. Additionally, from the 1970s onwards seven scoring systems have been proposed for the staging of endometriosis, whilst none for adenomyosis. Some workers [4, 26] have proposed their own classification systems, but none has been officially approved by scientific consensus. Among the various terms used to describe adenomyosis, the two most established ones are diffuse and focal. The diffuse form represents a uniformly thickened uterus that most commonly affects the

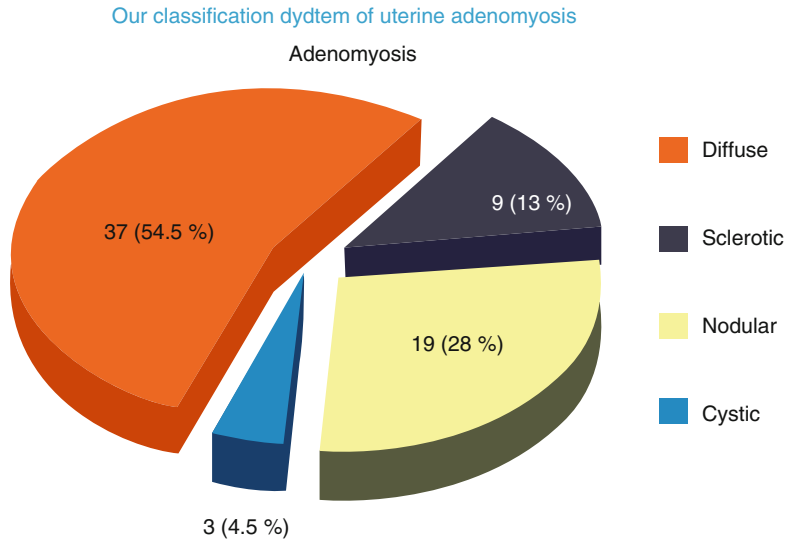

Fig. 7.1 Uterine adenomyosis: breakdown according to type (total 68 patients)

posterior myometrium. Focal adenomyosis or adenomyoma is a most obviously defined lesion that resembles a fibroid, with which it is also commonly confused. Out of the two, the most common form is the diffused lesion.

Our study involved the analysis of data from 68 women who had undergone operations at our centre over a 13 year period with histologically proven adenomyosis. The patient's age, history, physical examination, imaging recordings, operative findings, type of procedure performed and histology confirmation were necessary for inclusion. During our study, four distinct types of adenomyotic lesions were identified: the diffused lesion, the nodular type, the sclerotic lesion and the cystic lesion. Analytically, of 68 patients, 37 (54.5 %) had diffuse, 19 (28 %) nodular, 9 (13 %) sclerotic and 3 (4.5 %) cystic lesions (Fig. 7.1). The nodular, sclerotic and even the cystic types could have been grouped conveniently together as focal adenomyotic lesions.

Group A**. Diffuse adenomyosis** (Fig. 7.2)
mean age: 44.4 years (range 27–59)
presenting symptoms: menorrhagia, dysmenorrhoea
imaging: uniformly enlarge uterus, most frequently posterior area, commonly seen myometrial inclusion cysts
topography: uniformly enlarged uterus
intra-operative findings: spongiform enlarged uterus, myomata and deep endometriosis also found between 11 and 36 % of cases.

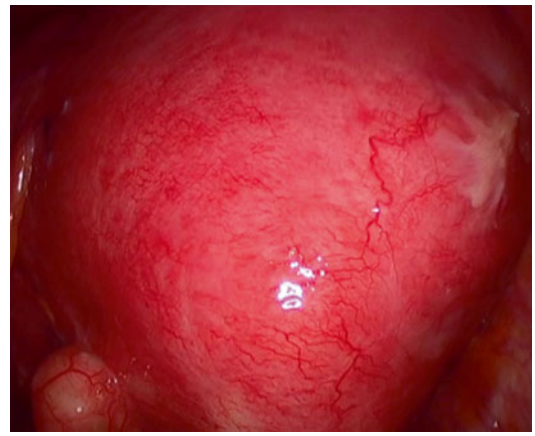

Fig. 7.2 Laparoscopic image of diffuse posterior adenomyosis

Group B**. Nodular adenomyosis** (Fig. 7.3)
mean age: 37.7 (range 27–45),
presenting symptoms: cyclic pain-dysmenorrhea disproportionate for the size of the lesion, resemble deep endometriotic nodules
imaging: spherical lesion resembling small myoma
topography: fundal – apical area near the round ligaments or the tubal isthmus,
intra-operative findings: firmly attached to serosa, no pseudo-capsule.

Group C**. Sclerotic adenomyosis** (Fig. 7.4)
mean age: 40.1 (range 30–47)
presenting symptoms: dysmenorrhea, menorrhagia and subfertility

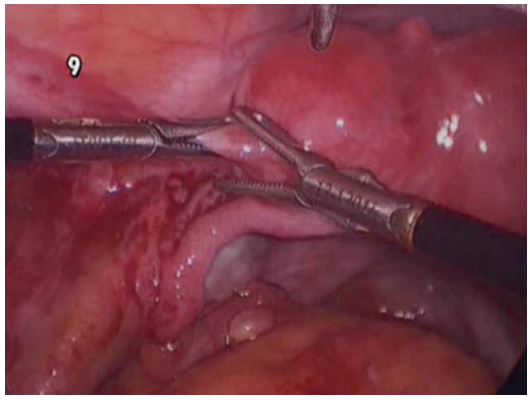

Fig. 7.3 Nodular adenomyosis close to left round ligament

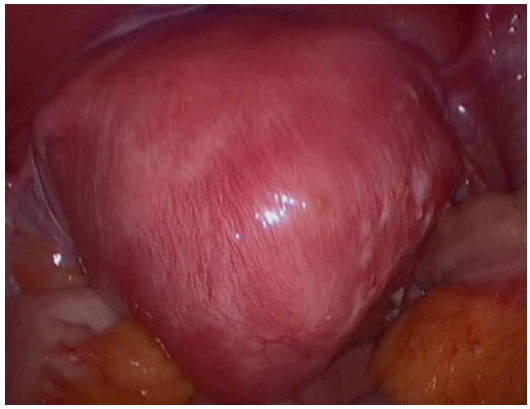

Fig. 7.4 Large posterior sclerotic adenomyoma

imaging: ill defined, irregularly shaped intramural mass, occasionally inclusion cysts, lacking the characteristic appearance of the myomatous pseudo-capsule.

topography: intra-mural lesion more often posterior uterine wall. Macroscopically resembles myoma

intra-operative findings: During excision the lesion has sclerotic whitish appearance, friable and difficult to grasp. Reduced bleeding, the lesion firmly attached to the serosa and to the endometrium

Group D**. Cystic adenomyosis** (Fig. 7.5)

mean age: 30.7 (range 28–33)

presenting symptoms: dysmenorrhea

imaging: large (>3 cm) intramural endometriotic looking cyst

topography: random intramural distribution. Primary cystic lesion (type II) of the adult needs to be distinguished from secondary iatrogenic lesion or the rarer form of juvenile cystic adenomyosis (type I) [27]

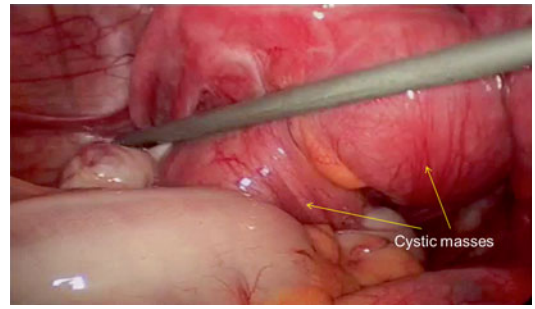

Fig. 7.5 Cystic adenomyosis

intra-operative findings: typical endometriotic like cyst, firmly adherent on surrounding myometrium

Symptomatology and Adenomyosis Types

There seemed to be significantly more patients with sclerotic $(p = 0.039)$ and nodular type $(p \leq 0.001)$ lesions complaining of severe dysmenorrhea compared with diffused adenomyosis. Although two out of the three patients with cystic lesions also suffered with pelvic pain, the difference with the other types of adenomyosis was not statistically significant possibly due to small number of patients with cystic lesions (Fig. 7.6).

Adenomyosis Types and Endometriosis and Fibroids

Fibroids and endometriosis occurred in a variable proportion with all types of adenomyosis. Myomas seemed to co-exist in 10 (27 %) with diffused, 4 (44 %) with sclerotic, 7 (37 %) with nodular and 1 (33 %) with cystic adenomyosis. Endometriosis occurred in 3 (8 %) of diffused lesions, 2 (22 %) sclerotic lesions, 3 (16 %) nodular lesions and 0 % in cystic lesions. in both fibroids and endometriosis cases there was not statistical significance between the four groups of adenomyosis lesions (Fig. 7.7).

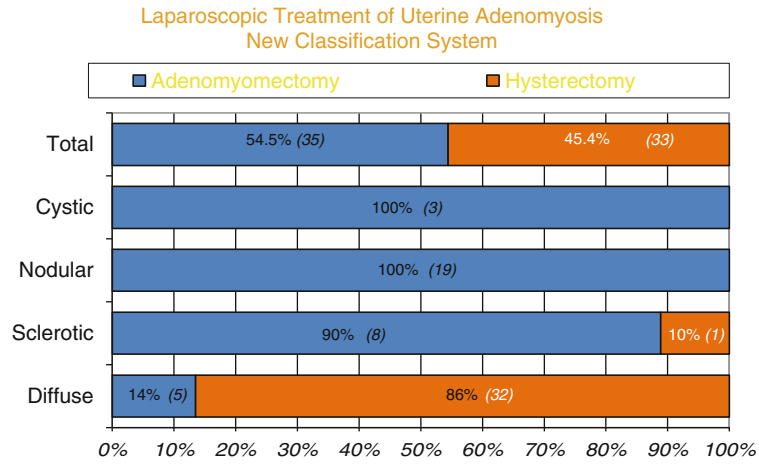

Fig. 7.6 Hysterectomy vs adeno-myomectomy: surgical outcome of the four adenomyosis type

Age and Adenomyosis Types

There seemed to be an age distribution of adeomyosis types with cystic lesions occurring in youngest age group, mean 30.7 years, nodular lesions, mean age 37.7, sclerotic lesions mean age 40.1 and diffuse mean age 44.4 (Fig. 7.8). Significant statistical difference was observed in the age onset between diffuse and nodular lesions $p \leq 0.001$ and diffuse and cystic lesions $p \leq 0.001$ (Fig. 7.9).

Therapy for the Four Different Types of Adenomyosis

Laparoscopic techniques for adenomyotic lesions

Diffuse Adenomyosis

When uterine preservation is required, this type of surgery presents an enormous challenge. Technically, a partial uterine resection has to be performed and this anatomically is a debilitating procedure. Most often what remains is a reduced organ with ambiguous functional capacity as regards fertility. This type of surgery is in reality a method of complete uterine reconstruction and patients should be warned about risks. Not only the resulting uterus has reduced reproductive capacity but the organ could rupture in a subsequent pregnancy! [28] Additionally, one needs to be prepared to face severe adhesions since a significant proportion of such patients have had previous surgery. The operative technique entails removing most of the affected myometrium and suturing together healthy tissue. It is of paramount importance that the pre-operative assessment of the lesion is conducted by the surgeon himself. In most cases the lesion cannot be removed en bloc and should be resected in a stepwise fashion, often having to "tunnel" under the uterine serosa in order to preserve as much uterine surface as possible. We inject the operative area with vasopressin and use mono-polar current to cut the tissue. Once the whitish fibrotic tissue is removed pinker and better blood supplied myometrium is found. It is vital to suture healthy tissue to healthy tissue and not to adenomyotic because the latter leads to defective healing. We have coined the acronym ***C.U.R.E.S.***, i.e. ***C****omplete* ***U****terine* ***R****econstructive* ***E****ndoscopic* ***S****urgery* when we refer to this type of massive adenomyosis resection (Fig. 7.10).

The massive uterine wounds that ensue from such resections have to be repaired in layers. We use long 40 mm atraumatic needles for the deep layers which we repair with 1 monocril sutures and 0–2.0 monocril for the serosal closure.

In our series, in only 5 (13.5 %) patients with diffuse adenomyosis was uterine sparing surgery possible in contrast with 7 (77.8 %) of women with sclerotic lesions. In the remaining cases

Fig. 7.7 Table with statistics used to compare adenomyosis types and symptomatology

	Diffuse (37)	**Sclerotic** (9)	**Nodular** (19)	**Cystic** (3)
Pelvic pain / Dysmenorrhoea	7 (**19 %**)	5 (**55 %**)	13 (**68 %**)	2 (**67 %**)
[Diff] vs [Scler]→ **Statistically Significant (P=0.039)** (Fischer Exact Test) [Nod] vs [Scler]→ Non Statistically Significant (Fischer Exact Test) [Diff] vs [Nod]→ **Statistically Significant (P≤0,001)**…(χ^2 test) (**Power** with alpha:0,050 **= 0.938)** [Diff] vs [cyst]→ Non Statistically Significant (Fischer Exact Test) [Scler] vs [Cyst]→ Non Statistically Significant (Fischer Exact Test) [Nod] vs [Cyst]→ Non Statistically Significant (Fischer Exact Test)				
Metrorrhagia	31 (**84 %**)	4 (**44 %**)	7 (**37 %**)	1 (**33 %**)
[Diff] vs [Scler]→ **Statistically Significant (P=0.025)** (Fischer Exact Test) [Nod] vs [Scler]→ Non Statistically Significant (Fischer Exact Test) [Diff] vs [Nod]→ **Statistically Significant (P=0,001)**…χ^2 test (**Power** with alpha:0,050 **= 0.922)** [Diff] vs [Cyst]→Non Statistically Significant (Fischer Exact Test) [Scler] vs [Cyst]→ Non Statistically Significant (Fischer Exact Test) [Nod] vs [Cyst] → Non Statistically Significant (Fischer Exact Test)				
+Fibroids	10 (**27 %**)	4 (**44 %**)	7 (**37 %**)	1 (**33 %**)
[Diff] vs [Scler]→ Non Statistically Significant (Fischer Exact Test) [Nod] vs [Scler]→ Non Statistically Significant (Fischer Exact Test) [Diff] vs [Nod]→ Non Statistically Significant (χ^2 test) [Diff] vs [Cyst]→ Non Statistically Significant (Fischer Exact Test) [Scler] vs [Cyst]→ Non Statistically Significant (Fischer Exact Test) [Nod] vs [Cyst]→ Non Statistically Significant (Fischer Exact Test)				
+ Endometriosis	3 (**8 %**)	2 (**22 %**)	3 (**16 %**)	0 (**0 %**)
[Diff] vs [Scler]→ Non Statistically Significant (Fischer Exact Test) [Nod] vs [Scler]→ Non Statistically Significant (Fischer Exact Test) [Diff] vs [Nod]→ Non Statistically Significant (Fischer Exact Test) [Diff] vs [Cyst]→ NonStatistically Significant (Fischer Exact Test) [Scler] vs [Cyst]→ NonStatistically Significant (Fischer Exact Test) [Nod] vs [Cyst]→ NonStatistically Significant (Fischer Exact Test)				
Hysterectomy	30 (**81 %**)	1 (**11 %**)	0 (**0 %**)	0 (**0 %**)
Adenomyomectomy	7 (**19 %**)	8 (**89 %**)	19 (**100 %**)	3 (**100 %**)

Fig. 7.8 Table of adenomyosis types and age groups

Total No of Cases of Adenomyosis: 68

Age: Mean: **41.2 yrs**, Standard Deviation: **6.7 yrs**, Min: **27 yrs**, Max: **59 yrs**

Cases of Cystic Adenomyosis: 3

Age: Mean: **30.7 yrs**, Standard Deviation: **2.5 yrs**, Min: **28 yrs**, Max: **33 yrs**

Cases of Diffuse Adenomyosis: 37

Age: Mean: **44.4 yrs**, Standard Deviation: **6.0 yrs**, Min: **27 yrs**, Max: **59 yrs**

Cases of Sclerotic Adenomyosis: 9

Age: Mean: **40.1 yrs**, Standard Deviation: **6.4 yrs**, Min: **30 yrs**, Max: **47 yrs**

Cases of Nodular Adenomyosis/Adenomyomas: 19

Age: Mean: **37.7 yrs**, Standard Deviation: **5.2 yrs**, Min: **27 yrs**, Max: **45 yrs**

total or subtotal hysterectomy was performed. The strongest indication for total hysterectomy is the presence of deep infiltrating endometriosis (DIE) affecting the cervix and recto vaginal septum (RVS). This is not an uncommon situation in cases of diffuse adenomyosis. If endometriotic nodules remain after surgery, dysmenorrhea will most likely persist! The use of anti-adhesive measures is currently being assessed in our centre but no substance has so far proven to be of significance in adhesion prevention.

Nodular Adenomyosis

This occurs more frequently in younger women who typically present with disproportionate dysmenorrhea for the type and size of their pathology. Nodular lesions are frequently located in the apical – fundal part of the uterus and are painful on palpation. During surgery these nodules are tenaciously adherent, like all adenomyomata, to the surrounding tissues. When they're removed they leave a noticeable defect on the uterine wall which is frequently located near the tubal isthmus (Fig. 7.11). Repair is not easy since tubal patency is mandatory and the wound edges are in close proximity to such structures. Vasopressin is also valuable in such cases because anastomotic vessels are often involved in such lesions.

Repair is ideally performed in two layers with 3.0 or 2.0 monocryl sutures in two layers with interrupted sutures. Subsequent pregnancies need careful follow-up. Symptoms of dysmenorrhea disappear soon after surgery. From our limited experience, it was surprising to note that women with nodular endometriosis did not have concomitant Deep Infiltrating Endometriosis (DIE) of the Recto Vaginal Septum (RVS).

Sclerotic Adenomyosis

Such lesions are notoriously mis-diagnosed for uterine myomas (Fig. 7.4). Expert sonographers can discriminate sclerotic adenomyotic lesions due to the irregular contour of such lesions, altered peripheral vascularization, lack of anatomical capsule and accompanying symptoms. Ideally the surgeon should be aware of this condition and be prepared before surgery. Thus we advise patients with any kind of uterine pathology to be assessed by the responsible surgeon before entering the OR.

The macroscopic appearance during surgery is similar to myomas unless the lesion is deep in which case the uterus is uniformly distended.

Comparison of age between groups [Diffuse] vs [Nodular] Adenomyosis:

One Way Anova & Tukey Test

Difference [(Diffuse)-(Nodular)]: 6.7 yrs

P<0,001

Power of test (with alpha= 0,05): 0.993

t-test

Difference [(Diffuse)-(Nodular)]: ***6.7 yrs***

95% C.I. (difference of means): ***3.40 –10.05*** *(yrs)*

P=<0,001

Power of test (with alpha= 0,05): ***0.982***

Comparison of Age between groups [Diffuse] vs [Cystic] Adenomyosis:

One Way Anova & Tukey Test

Difference [(Diffuse)-(Nodular)]: **13.74 yrs**

P=0,001

Power of test (with alpha= 0,05): **0.993**

t-test

Difference [(Diffuse)-(Nodular)]: ***13.74 yrs***

95% C.I. (difference of means): ***5.85 –20.30*** *(yrs)*

P=<0,001

Power of test (with alpha= 0,05): ***0.968***

Comparison of Age between groups [Diffuse] vs [Sclerotic] Adenomyosis:

One Way Anova & Tukey Test: NSS

Comparison of Age between groups [Sclerotic] vs [Nodular] Adenomyosis:

One Way Anova & Tukey Test: NSS

Comparison of Age between groups [Sclerotic] vs [Cystic] Adenomyosis:

One Way Anova & Tukey Test: NSS

Comparison of Age between groups [Nodular] vs [Cystic] Adenomyosis:

One Way Anova & Tukey Test: NSS

Fig. 7.9 Comparison of adenomyosis age groups, statistical methods and result

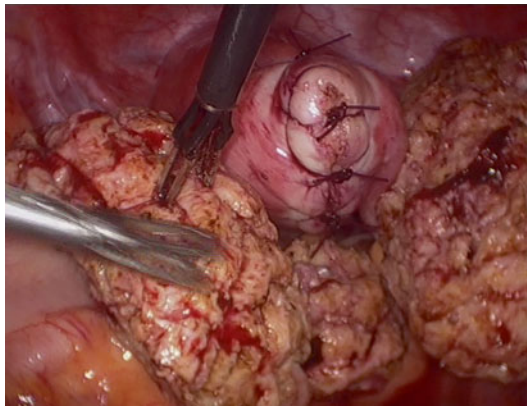

Fig. 7.10 C.U.R.E.S. Resection of posterior diffused adenomyosis with uterine repair. Most of the posterior fundal area is resected

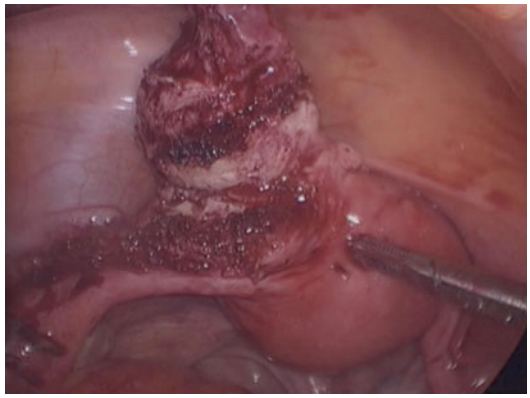

Fig. 7.11 Nodular lesion removed from left uterine horn

Visual palpation is useful in such cases. This is accomplished by pressing gently against the uterine surface with atraumatic forceps. Adenomyotic tissue, even if located deep under the surface, feels harder. This happens due to peripheral fibrosis that extends beyond and around the lesion. We promote the use of intra operative sonography to locate deep adenomyotic lesions. Vasopressin injection can be useful although, surprisingly, such procedures can be less haemorrhagic than myomectomies.

The resection technique involves incising the uterine serosa directly over the lesion and carrying on cutting deep into the lesion. Once the uterine incision is adequately opened the lesion is grasped with toothed forceps and resected in pieces. We find it easier to remove chunks of tissue, similarly to diffused lesions, rather than trying to remove the whole lesion at once. Frequently 'tunneling' under the uterine surface is necessary in order not to resect too much uterine wall. The healthy myometrium is identified firstly by noticing the change of color and texture of the tissue, i.e. from an off-white hard mass to a softer muscle like tissue. Secondly, adenomyotic lesions due to fibrosis tend to bleed less; this changes once healthy myometrium is reached which bleeds promptly.

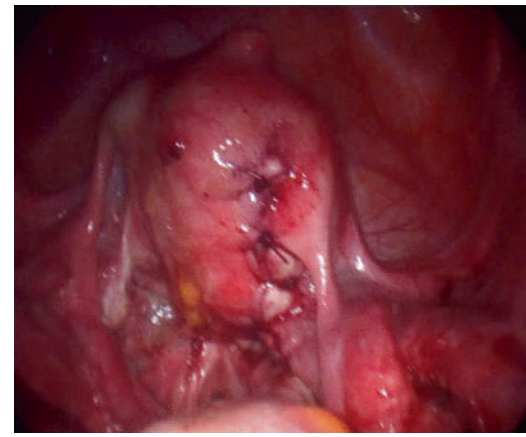

Fig. 7.12 Uterine repair following resection of posterior sclerotic adenomyosis

It is important to remove all foci of adenomyosis. Approximating and suturing diseased myometrium will result in defective healing. It is also wise to minimize the use of bipolar diathermy for haemostasis. Excessive myometrial burns promote further weakening of the uterine scar. The uterine wound is always repaired in layers using monocril 0 or 1 sutures for the deep layers and 0 or 2.0 monocril for the serosal closure (Fig. 7.12).

Cystic Adenomyosis

These lesions tend to occur to younger age groups and are typically accompanied by intensive dysmenorrhea. On ultrasound a typical endometriotc cyst can be seen within the myometrium. There is no typical distribution of such lesions, occurring in variable sites of the uterine body (Fig. 7.13).

In our series, the cyst occurred anteriorly in the supra-cervical region in one patient and in the lateral and posterior aspect of the uterus in the other two. In one case a large six centimeter adenomyotic cyst occurred following previous laparoscopic myomectomy during which a posterior myoma was excised. Following reassessment of the recording of the initial procedure it was noticed that the cavity was accidentally breached and poorly repaired. This resulted in a post-traumatic myometrial fistula with an inclusion iatrogenic adenomyotic cyst.

In all cases the whole of the cystic wall was resected with healthy apposition of uterine muscle. The wound was repaired in layers using 2.0 monocril sutures for the deeper layers whilst 3.0 monocril for the serosal closure.

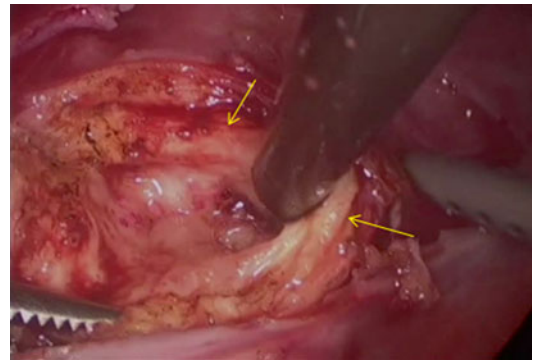

Fig. 7.13 Opened cystic lesion, the cystic wall is seen within the myometrium

Histopathology

Haematoxylin and eosin stains were used in paraffin blocks. These were obtained from the surgical specimens in order to histologically identify the adenomyosis lesions. This was followed by Masson trichrome stain (Goldner with light green) to study the collagen and the smooth muscle fibers surrounding the adenomyosis foci. (red for muscle fibers and green for collagen).

Histology revealed distinct differences between diffuse, nodular, sclerotic and cystic adenomyosis uteri.

1. **Diffuse adenomyosis** was identified histologically when scarse adenomyosis foci were observed within normal myometrium. Smooth muscle fibres with bundled growth pattern were recognized surrounding the lesion (staining red) Masson trichrome histochemical stain revealed only a few supporting collagen fibres (Fig. 7.14).
2. **Sclerotic adenomyosis** was identified histologically when scarse adenomyosis foci were observed within densely packed collagen fibres – most probably a degenerating phenomenon. The surrounding myometrium was normal or/and leiomyomatous (Fig. 7.15).
3. **Nodular adenomyosis** was histologically identified when scarse adenomyosis foci were observed within leiomyomatous tissue. Densely arranged smooth muscle fibres – probably due to reactive hyperplasia of the smooth muscle fibres – staining red (Fig. 7.16).
4. **Cystic Adenomyosis:** on gross examination, cystic endometriosis is characterized by the identification of large intramyometrial cystic spaces that might be haemorrhagic. Histology reveals an endometrioid type epithelial lining composed of a single layer of glandular cells with eosinophylic cytoplasm and round or elongated nuclei some of which might be hyperchromatic. Some amount of endometrial stroma can also be found. The whole cyst is surrounded by myometrial smooth muscle bundles (Fig. 7.17).

Conclusion

Uterine adenomyosis is a rather common disease, yet poorly understood. The cause of the problem lies in the 'illusional' state of this condition especially in its early expressions. Generally, the difficulty of reaching accurate diagnoses due to nonspecific symptomatology, poor sonographic criteria and clinical signs add to the problem. The picture is complicated by the lack of consensus on definition and staging of this condition.

Generally, although work and effort has been put in to determine the critical thickness of the JZ before adenomyosis can be correctly

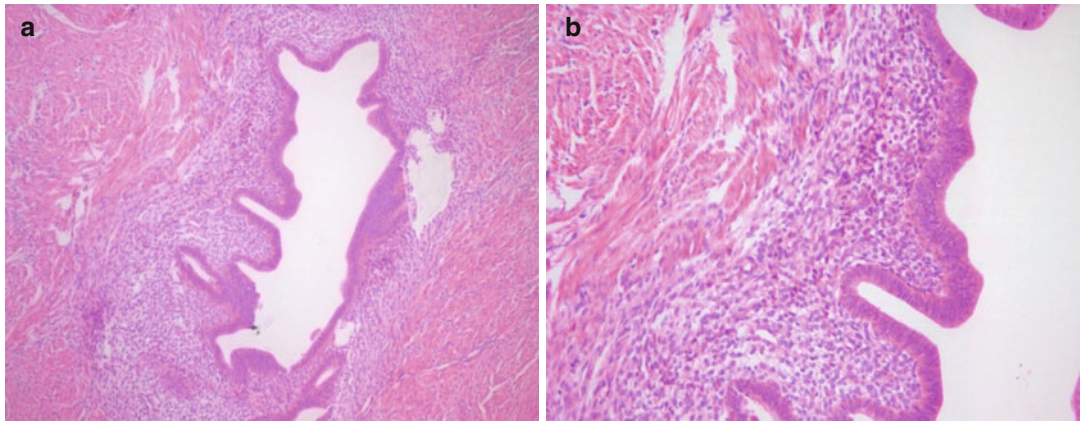

Fig. 7.14 Histology of diffuse adenomyosis (**a**) Multiple, variable sized foci of adenomyosis in the entire uterine wall, proliferative endometrium with abundant stroma. (**b**) Focus of adenomyosis with no hyperplasia of the smooth muscle cells of the uterine wall

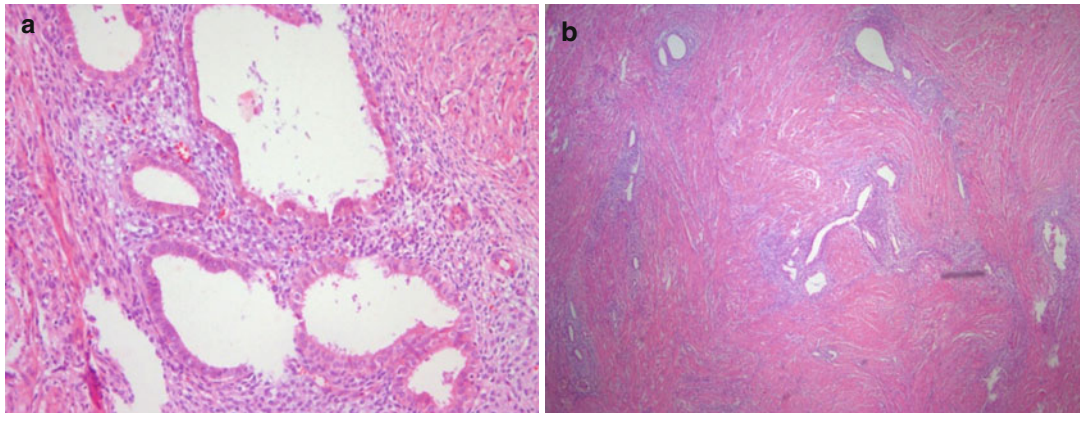

Fig. 7.15 Histology of sclerotic adenomyosis (**a**) Segment of myometrium with multiple, variable sized foci. (**b**) Adenomyosis foci and endometrium: eosinophilic metaplastic epithelium with abundant highly vascularised stroma and epithelioid stromal cells

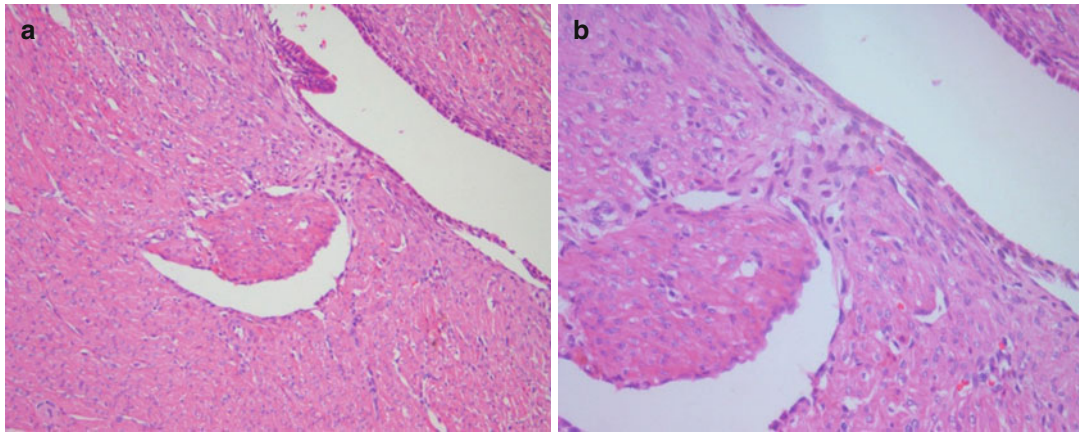

Fig. 7.16 Histology of nodular adenomyosis (**a**) Hyperplasia of smooth muscle cells of the uterine wall constraining the adenomyotic structure. (**b**) Flat epithelium with sparse stroma. Smooth muscle cell hyperplasia of the uterine wall

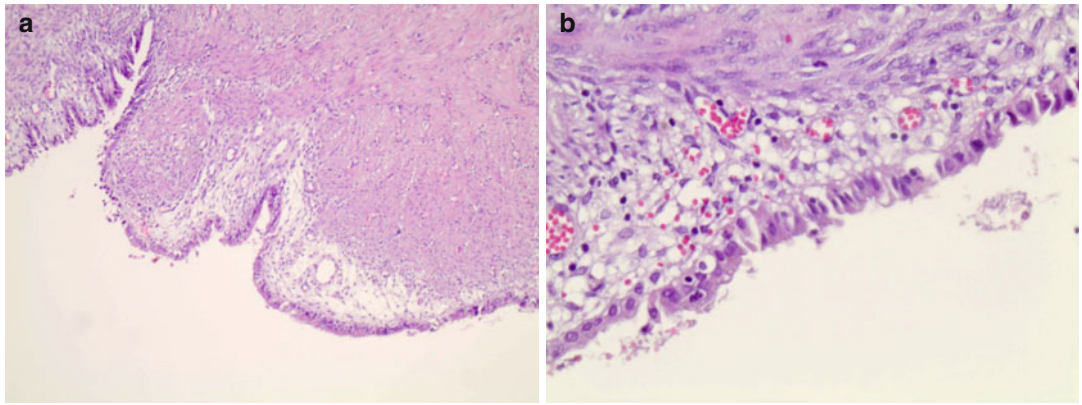

Fig. 7.17 Histology of cystic adenomyosis: (**a**) On low power examination the endometrioid type epithelial lining is separated by the myometrial smooth muscle bundles by a loose edematous stroma (H&E X100). (**b**) High power reveals the features of the epithelial cells and the loose stroma which is rich in small thin walled vessels (H&E X400)

diagnosed, little progress has been invested in studying the disease as a whole [20]. The depth of invasion does determine the severity of menorrhagia but does not explain the severe pain that small and endometrium unrelated lesions can cause. Neither of the proposed classification systems have considered the operability of such lesions. On the whole, several medical, surgical and miscellaneous treatments have been put forward but the effectiveness of each therapy is not entirely clear [25]. Adenomyosis symptoms, similarly to deep endometriosis, subside with GnRH analogues and progestogen therapies in either systemic or local application but in the long term do not solve the problem [29]. The significance of this misperception leads to delayed and occasionally incorrect decision making. Surgical miscalculations, especially in the patient with fertility problems, could result in suboptimal treatment and, in extreme circumstances, catastrophic results.

Diffuse adenomyosis, which affects the entire uterine musculature, is more likely to present with menorrhagia than segmental adenomyosis. Our results indicated that menorrhagia was indeed the chief complaint in cases that were classified as diffuse. On the contrary in women with nodular, sclerotic or cystic adenomyosis, pelvic pain and dysmenorrhea were the prominent symptoms. Therefore we suggest that adenomyotic lesions involving a limited area of the uterine body, that are of a more dense and fibrotic nature, are frequently associated with dysmenorrhea and pelvic pain. This finding correlates with the already reported relation of pain with disruption of tissue architecture caused by fibrosis in cases of deep endometriosis [30].

According to our experience, with diligent and careful preoperative assessment, uterine preservation was feasible in 54.5 % of all our patients. Whilst in diffuse adenomyosis a large majority, 86 %, of patients needed a hysterectomy; in sclerotic adenomyosis, uterine sparing surgery was feasible in 89.9 %. In all nodular and cystic cases the uterus was preserved (Fig. 7.17). One of the advantages of our proposed classification is that it can guide the treatment plan to less invasive procedures. We consider sclerotic adenomyosis an intermediate type of adenomyosis between diffuse and nodular which in the majority of patients can be managed conservatively. In our experience, pre-operative treatment with GnRH therapy did not affect the outcome of surgery. We find that their use should only be limited to patients requesting fertility with inoperable adenomyosis, just before their IVF treatment. In conclusion, the choice of uterine preservation in adenomyotic cases does not depend only upon the patient's wish but also on the

surgical skill and experience of the surgeon who is facing one of the most challenging operations.

With this classification we tried not only to distinguish adenomyosis in plainly defined clinical forms but, additionally, to assess the surgical feasibility and techniques for removing each of these lesions. Although uterine adenomyosis in its essence is a diffused or a confined lesion, its focal types seem to differ in topographic location, symptomatology, imaging appearance, patient age and histological findings. So, uterine adenomyosis should be further classified into (A), its most common form, which is the diffused type whilst focal lesions should be subdivided in (B) nodular, (C) sclerotic and (D) cystic adenomyosis.

References

1. Von Rokitansky C. Uber Uterusdrussen – Neubildung in Uterus – Ovarial Sarcomen. Ztsch K K Gesellsh Aerzte Wien. 1860;37:577–81.
2. Cullen TS. The distribution of adenomyomata containing uterine mucosa. Arch Surg. 1920;1:215–83.
3. Benagiano G, Brosens I. History of adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2006;20(4):449–63. Epub 2006 Mar 2.
4. Bird CC, McElin TW, Manalo-Estrella P. The elusive adenomyosis of the uterus–revisited. Am J Obstet Gynecol. 1972;112:583–93.
5. Von Recklinghausen F. Uber die Adenocysten der uterustumoren und Ubereste des Wolffshen Organs. Deutche Med Wochenscrift. 1893;19:824–6.
6. Cullen TS. Adenomyoma of the uterus. Philadelphia/London: W. B. Saunders Company; 1908.
7. Kossmann R. Abstamung der Druseneinschlusse in der Adenomyomen des uterus und der Tube. Arch Gynaecologie. 1897;54:381.
8. Ivanoff N. Uterusfibrom compliciert durch Sarcom und Carcinom. Monatsschr Geburtshilfe Gynaecol. 1898;5:295–300.
9. Meyer R. Eine unbekannte Art von Adenomyom des Uterus mit einer kritishschen Besprehung der Urnierenhypothese. v Recklinghauses Z Geburtshilfe Gynaecol. 1903;49:464–507.
10. Azziz R. Adenomyosis: current perspectives. Obstet Gynecol Clin North Am. 1989;16:221–35.
11. Leyendecker G, Wildt L, Mall G. The pathophysiology of endometriosis and adenomyosis: tissue injury and repair. Arch Gynecol Obstet. 2009;280:529–38.
12. Matalliotakis IM, Kourtis AI, Panidis DK. Adenomyosis. Obstet Gynecol Clin North Am. 2003;30:63–82, viii.
13. Ferenczy A, Bronsen I. Pathophysiology of adenomyosis. Hum Reprod Update. 1998;4(4):312–22.
14. Ota H, Igarshi S, Hatazawa J, et al. Is adenomyosis an immune disease? Hum Reprod. 1998;4:360–7.
15. Bergeron C, Amant F, Ferenczy A. Pathophysiology and physiology of adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2006;20:511–21.
16. Matsumoto Y, Iwasaka T, Yamasaki F, et al. Apoptosis and Ki-67 expression in adenomyotic lesions and in the corresponding eutopic endometrium. Obstet Gynecol. 1999;94:71–7.
17. Du H, Taylor HS. Stem cell and female reproduction. Reprod Sci. 2009;16:126–39.
18. Hricak H, Alpers C, Crooks LE, et al. Magnetic resonance imaging of the female pelvis: initial experience. Am J Roentgenol. 1983;141:1119–28.
19. Bulletti C, De Ziegler D. Uterine contractility and embryo implantation. Curr Opin Obstet Gynecol. 2006;18:473–84.
20. Gordts S, Brosens J, Fusi L, et al. Uterine adenomyosis: a need for uniform terminology and consensus classification. Reprod Biomed Online. 2008;17:244–8.
21. Dueholm M, Lundorf E, Hansen S, et al. Magnetic resonance imaging and transvaginal ultrasonography for the diagnosis of adenomyosis. Fertil Steril. 2001;76:588–94.
22. Exacustos C, Brienza L, Giovanni D, et al. Adenomyosis: three dimensional sonographic findings of the junctional zone and correlation with histology. Ultrasound Obstet Gynecol. 2011;37:471–9.
23. Benson RC, Sneeden VD. Adenomyosis: a reappraisal of symptomatology. Am J Obstet Gynecol. 1958;76:1044–57, 1057–61.
24. Peric H, Fraser IS. The symptomatology of adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2006;20:547–55.
25. Garcia L, Isaacson K. Adenomyosis review of the literature. J Minim Invasive Gynecol. 2011;18:428–37.
26. Levgur M, Abadi M, Tucker A. Adenomyosis: symptoms, histology and pregnancy terminations. Obstet Gynecol. 2000;95:688–91.
27. Takeuchi H, Kitade M, Kikuchi I, et al. Diagnosis, laparoscopic management and histopathologic findings of juvenile cystic adenomyoma: a review of nine cases. Fertil Steril. 2010;94:862–8.
28. Sizzi O, Rossetti A, Malzoni M, et al. Italian multicenter study on complications of laparoscopic myomectomy. J Minim Invasive Gynecol. 2007;14:453–62.
29. Bragheto A, Caserta N, Bahamondes L, et al. Effectiveness of levonogestrel-releasing intrauterine system in the treatment of adenomyosis diagnosed and monitored by MRI. Contraception. 2007;76:195–9.
30. Bonte H, Chapron C, Viera M, et al. Histologic appearance of endometriosis infiltrating uterosacral ligaments in women with painful symptoms. J Am Assoc Gynecol Laparosc. 2002;9:519–24.

Imaging of Myomas

8

Hans A.M. Brölmann, Wouter J.K. Hehenkamp, and Judith A.F. Huirne

Introduction

In its early days transvaginal ultrasound (TVU) scanning seemed to challenge clinical examination in the diagnosis of pelvic disorders as the accuracy of clinical examination was considered doubtful, especially in obese patients. Though the results were not univocal and the conventional vaginal examination has still its legitimate place [1, 2].

If fibroids are suspected in clinical examination, imaging enables the physician to visualize the separate fibroids, assess their size, number and topography in the uterus and their vascular characteristics. In the first place it is mandatory to distinguish fibroids from other histologic entities such as leiomyosarcoma, adenomyosis and solid ovarian tumours in particular since specimens in minimal invasive surgery may be ablated or removed by morcellation [3]. Secondly the relationship of the fibroid with the uterine cavity and the serosal surface should be determined. Women with symptomatic fibroids increasingly prefer treatment options that preserve the uterus, not only with regards to fertility but also from the awareness that hysterectomy may be overtreatment where selective treatment of the fibroids would suffice [4, 5]. Nowadays many minimal invasive treatment modalities are available or emerging such as myomectomy, hysteroscopic resection of submucous fibroids and ablation under imaging guidance. In all these procedures, the size and localisation are important for optimal surgical planning. These characteristics can be registered in a classification. The most well-known classification of submucous fibroids was published by Wamsteker and de Blok in 1993 where they demonstrated the relationship between the myometrial extension and fluid resorption during hysteroscopic electroresection [6, 7]. This classification typing submucous fibroids from 0 to 2 was further developed by Munro et al. [8] in order to classify all uterine fibroids, including the intramural and subserous. Next to the classification (relation to the uterine cavity and serosal surface) also the volume of the fibroid predicts operability in minimal invasive surgery.

Unless a fibroid is calcified, X-ray including CT is of little help in the diagnosis of fibroids as they are not well distinguished from their surroundings [9, 10]. Moreover, although the access to CT is better than to MRI, the ionizing radiation is considered a disadvantage.

On the other hand ultrasound and Magnetic Resonance imaging are excellent imaging techniques to visualize uterine fibroids. Ultrasound is readily available and often performed by the gynaecologist on routine basis during the

H.A.M. Brölmann, MD, PhD (✉)
W.J.K. Hehenkamp, MD, PhD
J.A.F. Huirne, MD, PhD
Department of Obstetrics and Gynaecology,
VU University Medical Centre, De Boelelaan 1117,
Amsterdam 1181HV, The Netherlands
e-mail: h.brolmann@ziggo.nl

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gynaecological examination, thereby combining medical history and physical findings with the images to enable the most adequate interpretation. It has however been shown that the interobserver agreement of ultrasound is lower than that of MRI [11]. Possible reasons are the lower resolution of ultrasound compared to MRI, but also the lack of well-defined criteria and the simultaneous real time scanning, operating the ultrasound machine and communicating with the patient, may affect reproducibility. Since the beginning of this century three dimensional ultrasound (3D US) is commercially available [12]. 3D US volumes can be stored on the hard disk of the ultrasound machine or of a personal computer. With the proper software images can be evaluated at a later stage, independently from the actual US examination or the patient. The software enables inspection of the region of interest (ROI) in all possible planes of which the rendered coronal plane is particularly useful in visualizing the uterus. Retrospective multislice analysis of the ROI, measurement of suspected lesions and quantitative Power Doppler improve the interpretation setting and may allow a more accurate diagnostic result.

We have chosen to divide the chapter in subheadings of available and appropriate imaging techniques and of the relevant clinical issues, such as functional histologic diagnosis, volume measurement, classification and vascularity.

Imaging Techniques Suitable for Fibroid Examination

Ultrasound

A piezo-electrical element (e.g. quartz) is capable of transforming an electrical impulse into ultrasonic waves and vice versa. In ultrasound imaging high frequency sound waves are emitted by the piezo electrical element and reflected against the tissue, depending of its characteristics. While audible sound as wavelengths ranging from 40 to 15,000 Hertz (Hz), ultrasound wavelengths are ranging from 1 to 10 MHz (1 Mega Hz is 1 million Hz). Higher frequencies, thus shorter wavelengths result in less penetration of the signal, but in a higher resolution. Therefore the frequency of the transabdominal ultrasound probe is lower, ranging from 2 to 5 MHz while the transvaginal ultrasound probe which is closer to the region of interest has higher frequencies (5–7 MHz).

Three Dimensional Ultrasound (3D US)

Special 3D probes emit ultrasound waves while changing the scan angle (‘sweep’) and receiving the reflected waves from a segment of the tissue thus taking a 3D tissue ‘sample’. The sweep is in most transducers mechanically driven, but recently the matrix array transducers ‘sweep’ without moving parts in the transducer, allowing a higher 3D frame rate per second. The collected volumes can be stored and examined in a later stage on the ultrasound machine or on the computer. Rendering every possible scanning plane from the volume, given it contains the proper structures, is a distinct advantage compared to 2D vaginal scanning (Fig. 8.1). Volumes are measured more accurately than in 2D scanning and the relation between fibroid and uterine cavity and serosal surface can be assessed more accurately as well.

The image volumes can be examined in different modes: three perpendicular planes are depicted on one screen next to the 3D image, of which the ‘box’ can be defined during examination. By rotating the three perpendicular axes (x, y and z) and scrolling through the reference slices the examiner can visualize the region of interest in every possible plane (Fig. 8.2). In the rendered (not directly scanned) planes there is some loss of resolution. Multislice technology enables the ultrasonographer to perform a tomographic analysis of the images. To measure volumes the Virtual Organ Computer-aided Analysis (VOCAL) software is used, which is explained elsewhere in this chapter. In obstetrics the use of 3D US is popular because of the surface mode, which enables visualizing the fetal face.

Although in gynaecology solid proof of the additional value of 3D US is lacking, there is some evidence that submucous fibroid

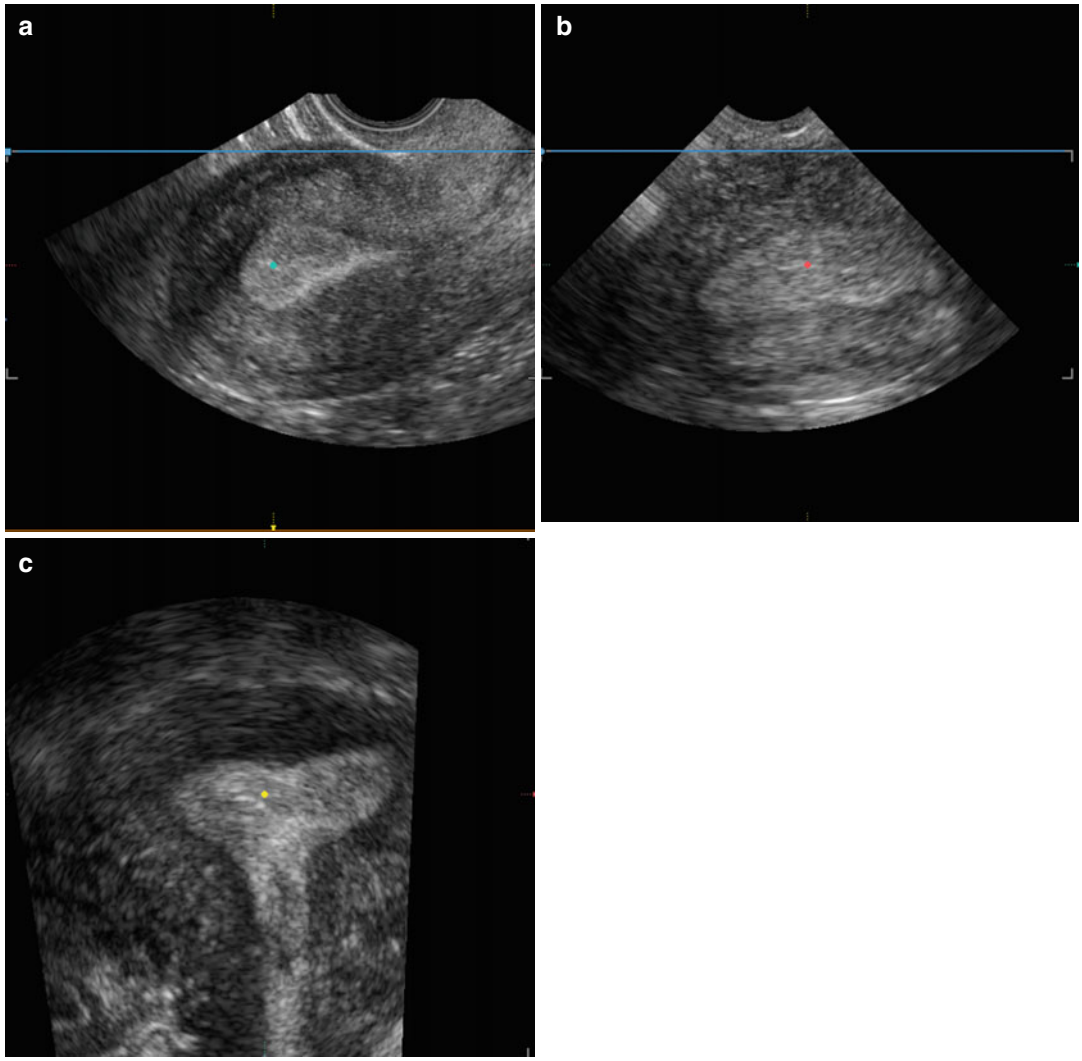

Fig. 8.1 transvaginal ultrasound of a T-shaped uterus in the sagittal plane (**a**), the transversal plane (**b**) and the coronal plane (**c**)

classification is more accurate in 3D than in 2D [13, 14]. Given the unfamiliarity of gynaecologists with retrospective 3D image analysis it is important to formulate strict criteria on interpretation in order to improve reproducibility and accuracy [15].

Power Doppler

The changing wavelength of sound from a moving surface or reflected by it is discovered by Andreas Doppler in 1842, a phenomenon which is named after him. In this way vessels can be visualized and characteristics of fluid flow can be evaluated. Two parameters can be measured in Doppler ultrasound (PDUS): the wavelength shift and the amplitude (power). Measurement of the wavelength shift expresses the velocity and the direction of the beamed particles, e.g. blood cells, while the amplitude expresses the volume of the moving particles. By measuring the velocity in the pulsating blood flow the resistance in a vessel can be assessed as well as the related pulsatility. Moving pixels are depicted in colour, where the colour represents the direction and the

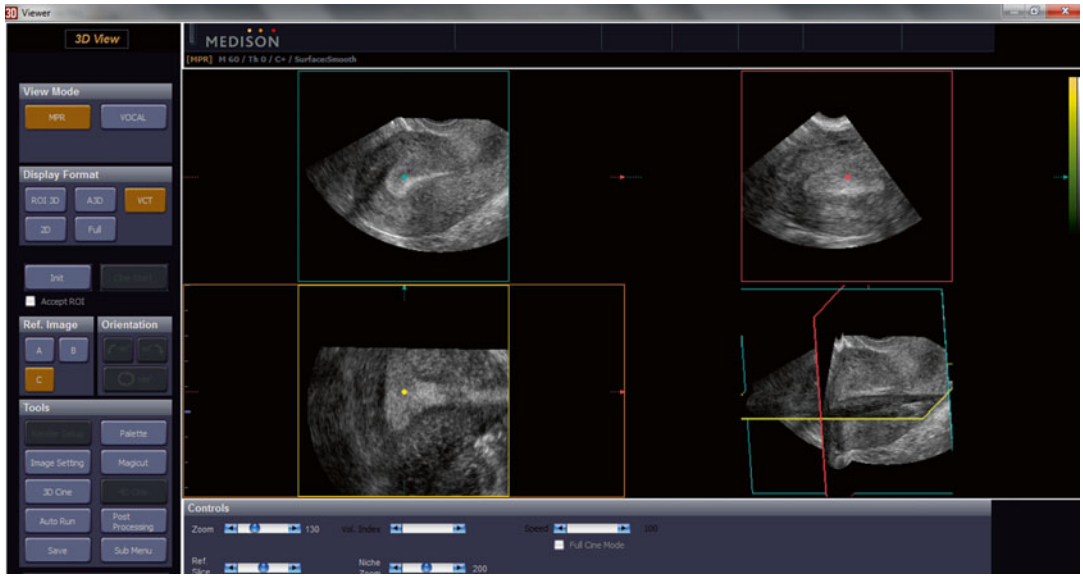

Fig. 8.2 screenshot in the software program Sonoview Pro™ of the uterus of Fig. 8.1 in MPR mode

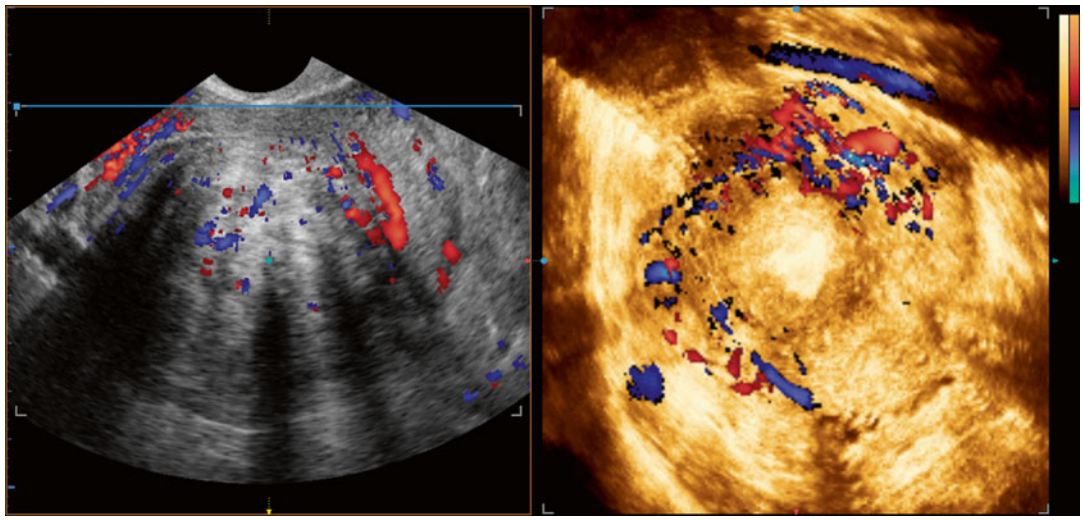

Fig. 8.3 Vessels around a fibroid with ultrasound greyscale combined with colour doppler

velocity of flow. The flow characteristics such as resistance index, pulsatility index and peak systolic velocity of single vessels can be measured (Fig. 8.3). In Power Doppler Ultrasound (PDUS) the processor time consuming wavelength shift is not calculated and movement is only visualized in terms of amplitude, which expresses the intensity of flow. PDUS is more sensitive in detecting blood flow in small vessels and is increasingly used to assess vascularity in tumours, also in gynaecology.

3D Power Doppler Ultrasound

In three dimensional Power Doppler (3D PD) moving particles are depicted in colour and the intensity (amplitude) of flow is measured in

a sampled volume of the region of interest. The coloured flow in the vessels enables the sonographer to evaluate the vessel pattern which can be related to the nature of the tumour. Moreover, by dividing the colour voxels (smallest ultrasound volume unit) by the total number of voxels, 3D PD estimates the vascularity and intensity of flow in the tissue expressed as vascularity index (VI), flow index (FI) and vascular flow index (VFI) [16]. The conventional power Doppler which is based on echo amplitude, allows better visualization of low flow than colour Doppler, but there are still blooming artefacts. To circumvent these disadvantages a new Doppler ultrasonographic technique, known as high-definition flow (HDF), has recently been introduced [17]. HDF has the potential benefits of better axial resolution, fewer blooming artefacts, and improved sensitivity to small vessels compared with colour and power Doppler. The main aspect of HDF is the use of short broadband pulses, which considerably improves the axial resolution. Recent software improvements allow calculation of these 3-dimensional (3D) indices using HDF rather than power Doppler imaging [18]. The validation of 3D PD is under way, but not self-evident. Differences in systolic and diastolic blood flow, the ultrasound machine settings (e.g. gain) and the definition of the region of interest all affect the reliability and validity of the measurements [18].

Saline or Gel Infusion Sonography (SIS or GIS) or Sonohysterography

In order to enhance contrast of the uterine cavity with the endometrial lining, the cavity can be instilled with saline or gel. The surface of the cavity is clearly depicted and the diagnostic accuracy of SIS in detected focal lesions such as polyps and fibroids is comparable with that of hysteroscopy [19]. In addition SIS has the advantage to look into the myometrial wall and gives more information about other (uterine) abnormalities. In transvaginal 2D scanning it has been shown that the intracavitary position of fibroids can be overlooked if compared with SIS [20]. Recently the saline was replaced by gel which sustains the distension of the uterine cavity for at least 10 min [21]. The 3D SIS of the uterine cavity enables thorough inspection of the cavity wall and is referred to as 'virtual hysteroscopy' [22] (Fig. 8.4).

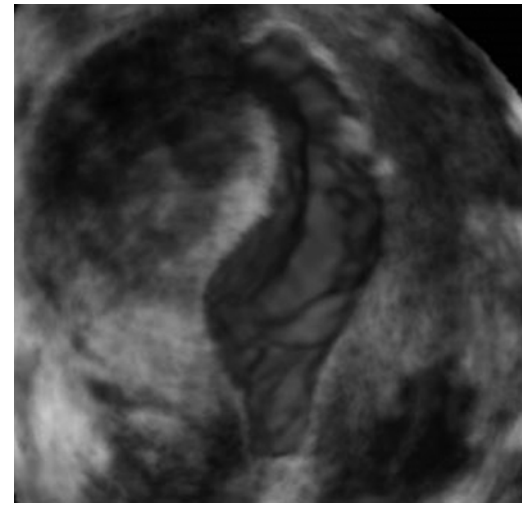

Fig. 8.4 3D image of saline infusion sonography (SIS) in uterus with submucous fibroid

Contrast Enhanced Ultrasound (CEUS)

As power Doppler is not able to pick up blood flow in vessels below 2 mm diameter, it is not suitable to estimate micro vascularity in the tissue. To assess micro vascularity the CEUS technique, although still experimental, is more appropriate [23]. In CEUS imaging micro bubbles contrast agents are injected intravenously. The micro bubbles measure 2–6 μm, have a wall thickness of 10–200 nm are filled with gas (perfluorocarbon or sulphur hexafluoride). After rupture of the micro bubbles the gas is exhaled after 10–15 min, while the shell components are metabolised by liver or kidney. By high-transmit-power insonation the micro bubbles can be destructed. Progressive refilling of the imaged volume is used to discriminate between contrast and tissue.

The results of CEUS in fibroid imaging are preliminary and show a possible beneficial effect evaluating and optimizing treatment effect of fibroid ablation or uterine artery

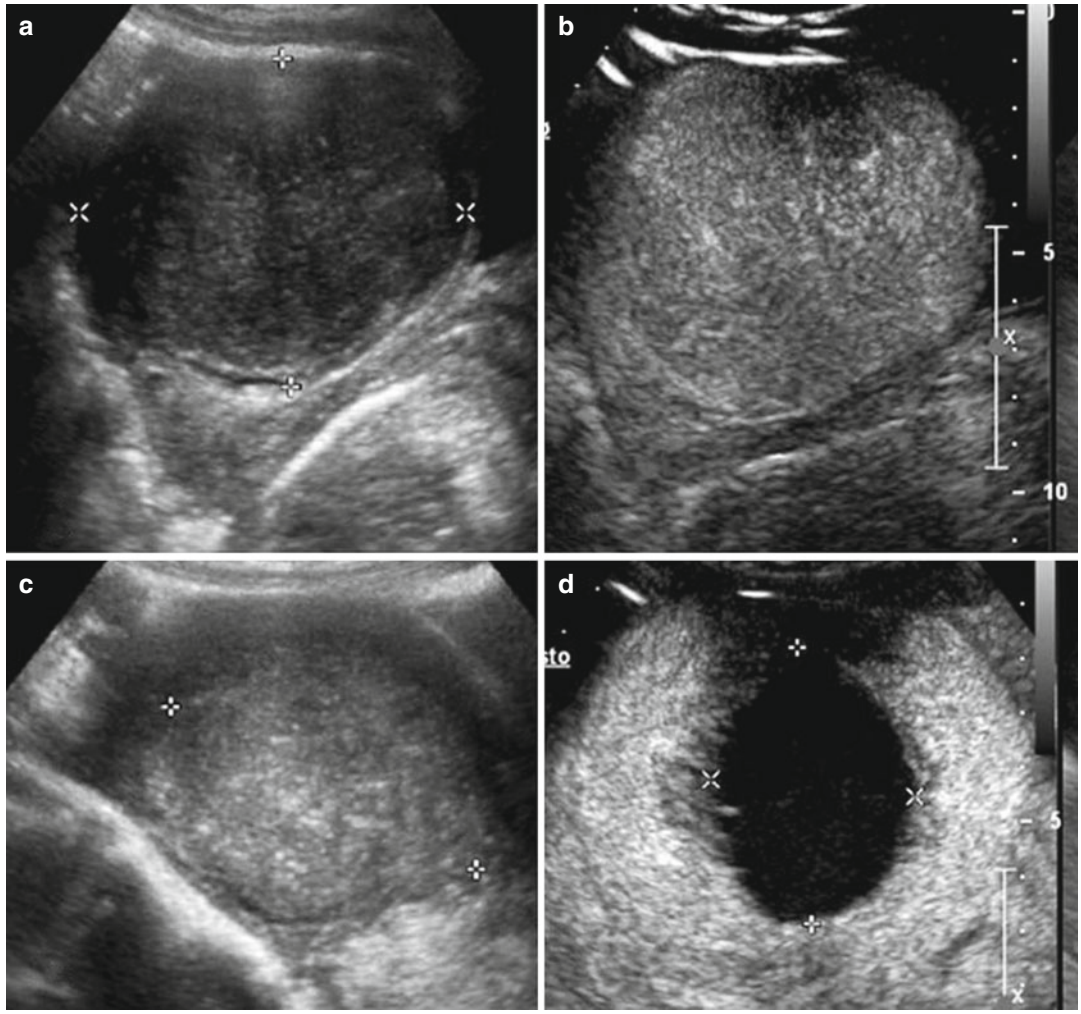

Fig. 8.5 Contrast Enhanced UltraSound (CEUS) of 7-cm symptomaticuterine fibroid. (**a**) B-mode ultrasound shows a hypoechoic mass in the uterus. (**b**) CEUS confirms rich vascularization inside the mass. (**c**) B-mode US 6 months after percutaneous RFA: the treated fibroid appears non-homogeneous and reduced in size. (**d**) CEUS confirmed a huge area of necrosis with a peripheral rim of enhancement in a normal uterus without any residual disease [71] (With kind permission from Springer Science+Business Media)

embolization [24, 25]. Also CEUS may help to discriminate leiomyosarcomata from fibroids [26] (Fig. 8.5).

Elastography

Elastography, first described by Ophir in 1991 [27], estimates differences in tissue stiffness or elasticity and could therefore be considered as image guided palpation. In physics the elasticity is expressed as Young's modulus (stress/strain). However in ultrasound elastography only strain is measured as the applied stress within the tissue is more or less the same. Strain is the distance between two positions of a predefined point in the tissue with and without compression. Compression is generally applied with the ultrasound probe, although also pulsating vessels or a vibro-acoustic stimulus may be used as a compression source. A color, according to the registered strain, is overlaying the ultrasound grayscale image. In this way it is comprehensible that a stiff nodulus becomes visible (dark or blue)

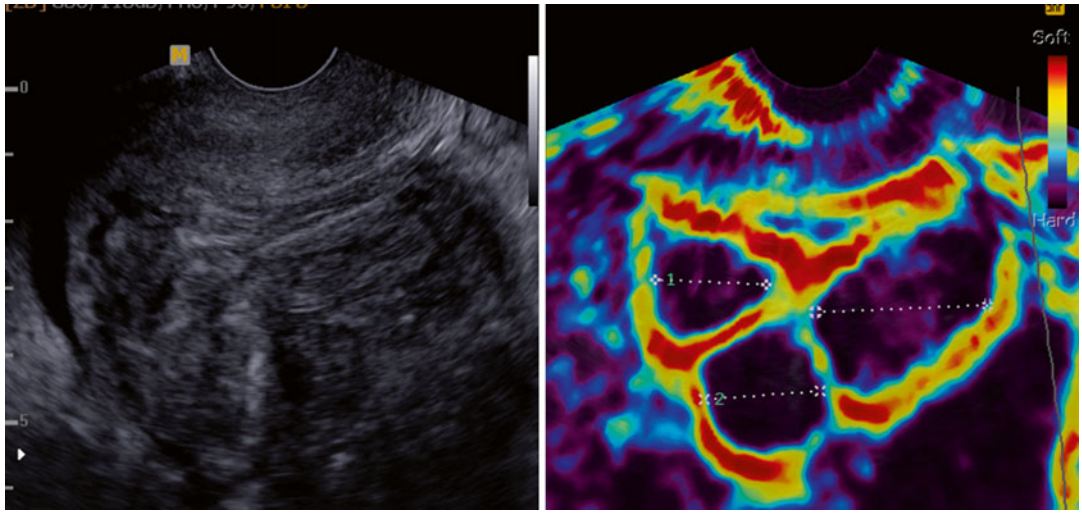

Fig. 8.6 Uterus with three fibroids visualized by elastography and greyscale ultrasound

in soft fatty tissue (yellow or red). Promising results have been reported in abnormalities in assessment of tumors in the breast, the prostate and the liver. In gynaecology elastography is reported in patients with fibroids, adenomyosis and cervical cancer [28, 29]. Elastoscanning may particularly be useful in patients with presumed fibroids, since it can depict number, outline and relation of the fibroid to cavity and serosal surface, making the fibroid classification more reliable (Fig. 8.6).

Drawback of the technique is the lack of standardization or calibration as it is impossible to deliver the same amount of compression during examination. This makes it impossible to compare elastographic results between different sessions in the same patient or between patients.

Magnetic Resonance Imaging (MRI) Scan

A good description of how Magnetic resonance imaging (MRI) works is published by Berger [30]. MRI uses the body's natural magnetic properties to produce detailed images form any part of the body. For imaging purposes the hydrogen nucleus (a single proton) is used because of its abundance in water and fat. The patient in the MRI is placed in a strong magnetic field which creates a magnetic vector as all protons' axes line up. Additional energy (radio wave) causes the hydrogen nuclei to resonate. When the radiofrequency source is switched off, the magnetic vector returns to its resting state which causes emission of a radio wave signal. This signal is used to create MR images. Two types of MRI are used depending on the tissue, T1 and T2 where T1 produces signal intensity of fat and blood and T2 of fluid and mucus. As Computed (Axial) Tomography (C(A)T) scan is able to produce a scan in several minutes visualizing bony structures as well as soft tissues, the MRI shows much higher detail in soft tissue imaging and is used in brain, spinal cord, tendons and ligaments and the pelvic organs. In gynaecology MRI is particularly useful for depicting fibroids, endometriosis and adenomyosis.

Positron Emission Tomography (PET) Scan

In a PET scan a gamma probe measures the positron emission of the tissue and visualizes it. Hereto a radionuclide is injected. A radionuclide is a radioactive tracer tagged to a natural chemical, such as glucose, water or ammonia. The natural chemical is selected for its metabolization in the tissue of interest. As malignancies in general

consume much glucose, the radionuclide fluorodeoxyglucose (FDG) is used for the depiction of the malignant tissue. The gamma radiation is produced when the radionuclide is broken down by emitting the positrons. The computer analyses the gamma rays and uses the information to create an image map of the organ or tissue being studied. In modern machines the 3D PET images overlay a CT scan to properly localize the structure of interest. PET scanning is used to rule out or monitor treatment of brain disorders as neoplasms, Alzheimer's disease, Parkinson's disease, but also disseminated cancer and to assess myocardium perfusion.

Also in gynaecology PET scanning is used e.g. in order to identify the nature of uterine tumours [31].

Diagnosis of Fibroids

Especially in case of intended conservative treatment of fibroids with medication, ablation or myomectomy or in case of intended morcellation, it is important having ruled out leiomyosarcoma or Smooth Muscle Tumour of Uncertain Malignant Potential (STUMP). As it is the professional standard to remove malignant tumours completely, it is not in the interest of cure to offer minimal invasive or conservative treatment of suspect lesions. Also the distinction between fibroid and adenomyoma is essential information because the latter is ill defined and can usually not be removed surgically without severe damage to the uterus. Imaging of the fibroids will therefore contribute to the proper diagnosis.

Leiomyosarcoma and STUMP

Uterine sarcoma is a mesenchymal tumor that can originate from smooth muscle cells (leiomyosarcoma) or from endometrial stroma (mixed Müllerian tumor or endometrial stroma sarcoma). The leiomyosarcoma (LMS) may appear similar to the leiomyoma (fibroid) and is therefore a confusing element in the diagnosis of fibroids. In general it was hypothesized that LMS is not originating in a fibroid but develops from a primary malignant cell line, but recently four cases of LMS originating in a normal fibroid were reported [32]. The risk of finding a sarcoma in a presumed fibroid ranges from 0.2 to 0.49 %. See Table 8.1 [33–37].

Table 8.1 Prevalence of sarcoma in presumed fibroids

Author	Year	No. of fibroids	No. of sarcomas	%
Seki	1992	1,886	7	0.37
Parker	1994	1,332	1	0.23
Leibsohn	1999	1,492	7	0.49
Seidman	2012	1,091	2	0.2

The most important criterion in the diagnosis of LMS is the number of mitoses found in active parts of the smooth muscle tumor. A common cut off level is over 5 mitoses in 10 high power (400×) fields [32, 38]. Other common characteristics of LMS are tissue necrosis, nuclear pleomorphism and vascular invasion. Patients with LMS are more often older and have larger tumours which are mostly solitary compared to patients with fibroids. Rarely the diagnosis is made with endometrial tissue sampling, but only so in case of abnormal uterine bleeding. Contrary to common belief, rapidly growing uterine tumours bear no additional risk of LMS as was reported by Parker in 1994 [35].

Ultrasound greyscale imaging of potential LMS is focussed on the lesion's margins and the presence of lacunae, which is a sign of necrosis (Fig. 8.7a). With these criteria up to 95 % of cases was reported to be detected [39]. The 2D power Doppler criteria pulsatility and resistance index and the peak systolic velocity, though changed in sarcomata, seem to have poor prognostic value [40]. However the finding of increased periferal and central vascularisation resulted in high sensitivity (100 %) at the cost of specificity (88 %), resulting in a high negative predictive value (100 %) and a predictive value of a positive test of 18 % [41] (Fig. 8.7b). The 3D PD has not yet been studied in the distinction between LMS and fibroids, but in a recent report the vascular indices correlated with cellularity in the fibroid, which may be associated with LMS and STUMP [43].

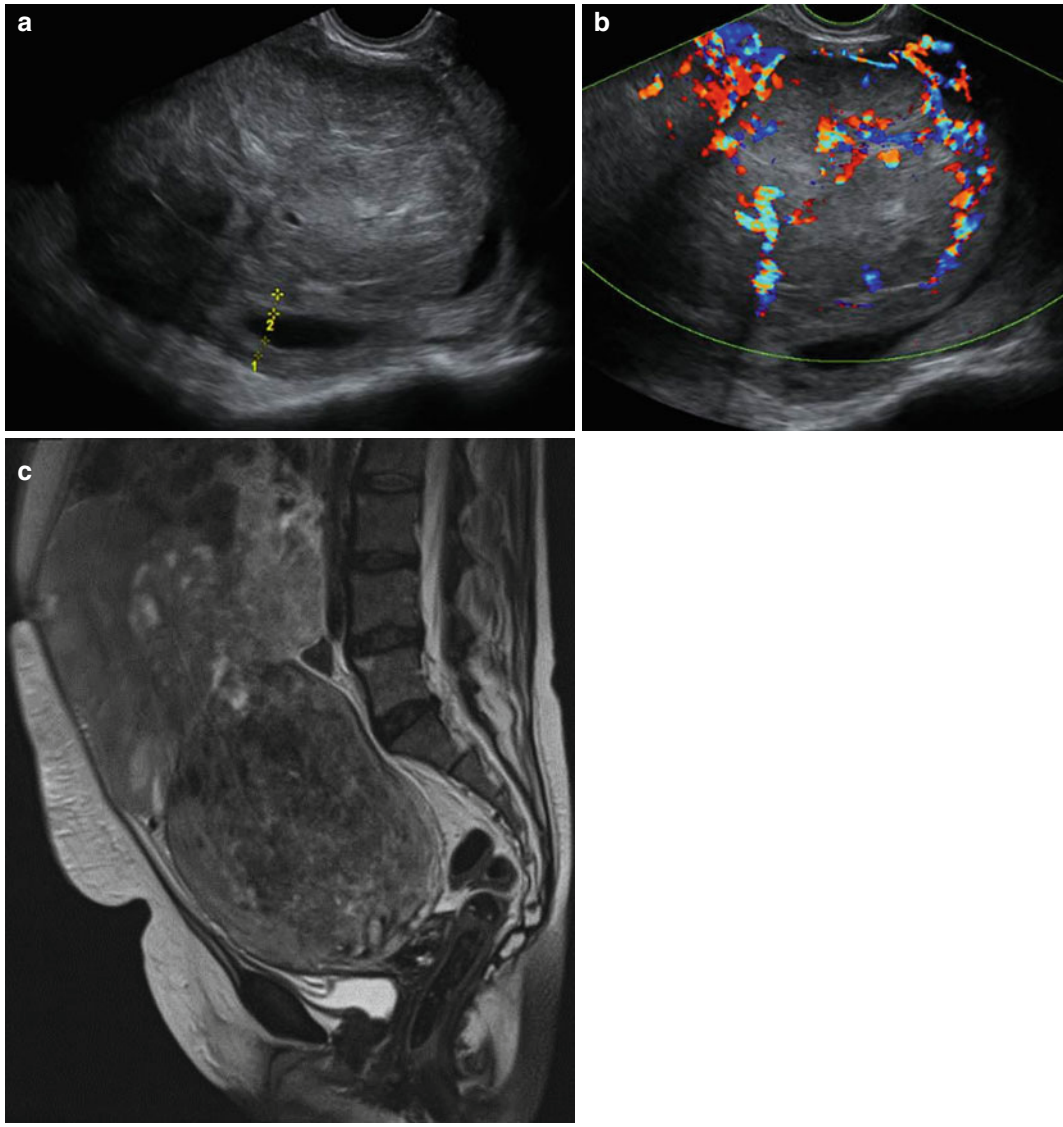

Fig. 8.7 (**a**) Greyscale ultrasound scan of uterus with leiomyosarcoma. The endometrial thickness is measured between the markers. 1 and 2 show the measurement of both endometrial layers. Besides fluid in the uterine cavity several lacunae can be seen. (**b**) Ultrasound greyscale image of leiomyosarcoma (same patient as in **a**) with color doppler. Note the abundant vascularity of the LMS, which is highly unusual in leiomyomas. (**c**) MRI image of large leiomyosarcoma with areas of necrosis (by courtesy of Thierry van den Bosch)

The value of MRI in the diagnosis of LMS is well established although absolute certainty cannot be achieved. As the incidence of LMS is low, most clinical studies of the diagnostic accuracy of MRI are underpowered. In general LMS shows more high signal areas on the T2 (Fig. 8.7c) than fibroids and a characteristic of LMS is the well demarcated, unenhanced pockets in dynamic MRI with the use of contrast. This feature was seen in 9/12 patients with LMS or STUMP and in 0/12 patients with fibroids [43].

The Positrone Emission Tomography has a place in the diagnostic armentarium of presumed fibroids. In PET scanning a radionuclide (tracer) on a biologically active molecule is visualized. In imaging of fibroids usually fluodeoxyglucose

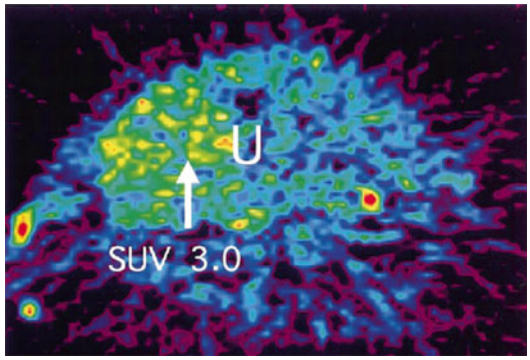

Fig. 8.8 PET scan of leiomyosarcoma. With a Standard Uptake Volume (*SUV*) of 3.0 (*white arrow*) malignancy has become more likely [44] (With permission from Elsevier)

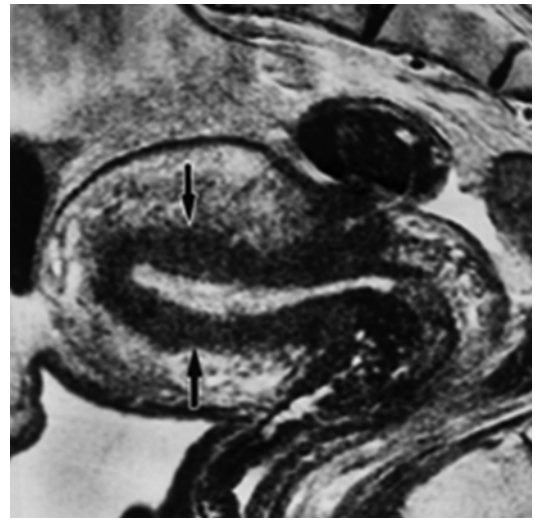

Fig. 8.9 T2 MRI of uterus with diffuse adenomyosis (*black arrows*)

(FDG) is used, but also other molecules, such as deoxyfluorothymidine (FLT) or alphafluorobetaoestradiol (FES) have been reported. In general the uptake of FDG in a fibroid is associated with the estrogen status, cellularity and the presence of malignancy. The result of the PET-scan is displayed in a three dimensional image, often combined with a CT overlay and expressed in Standard Uptake Value (SUV) (Fig. 8.8). In one study the mean SUV in fibroids was higher (1.39 ± 0.65) than in myometrium (1.24 ± 0.33) [44]. In another study [45] of 5 sarcomas the mean SUV was 4.5 ± 1.3. Generally a SUV of 2.0–3.0 is considered the cut off level for presumed fibroid becoming suspicious for sarcoma. FES may be more accurate in distinguishing LMS from fibroids than FDG, with an accuracy of resp. 93 and 81 % [46]. By calculating the rate between two different uptake molecules, e.g. FDG and FES, the test characteristics of PET can improve as well [47]. Only the retrospective study of Umesaki [45] compares different imaging techniques in case of suspected uterine sarcoma. Of the 5 sarcomata all were detected by FDG PET, 4 by dynamic MRI and 2 by Power Doppler ultrasound. Nevertheless, in case of clinical suspicion of uterine sarcoma the less invasive imaging modalities are first choice: grey scale ultrasound, dynamic MRI and PET. The role of image guided biopsies is not completely clear. Although the predictive value of a negative biopsy might be expected to be low because of the large area's of necrosis, an excellent negative predictive value is reported using MRI guided needle biopsies and Bell's classification on histology [48] with a cut off level of 2 [49]. No data are found on the possible spreading of sarcoma cells by multiple puncturing of the sarcoma.

Adenomyosis

Adenomyosis consists of endometrial glands in the myometrium that do not communicate with the uterine cavity. The endomyometrium is more hypoechoic than the periferal myometrium and is called the junctional zone. Diffuse adenomyosis is characterized by a thickened junctional zone (cut off level in general >12 mm) around the uterine cavity (Fig. 8.9). The uterine adenomyoma is a mass of focal adenomyosis not necessarily making contact with the junctional zone. The adenomyoma in particular may sometimes difficult to distinguish from the uterine fibroid as it has a similar appearance (Fig. 8.10). It may cause similar symptoms as heavy menstrual bleeding and features such as enlargement of the uterus and deformation of the uterine cavity. Adenomyosis is a common cause of failure of the endometrial ablation and of myomectomy if mistaken for a

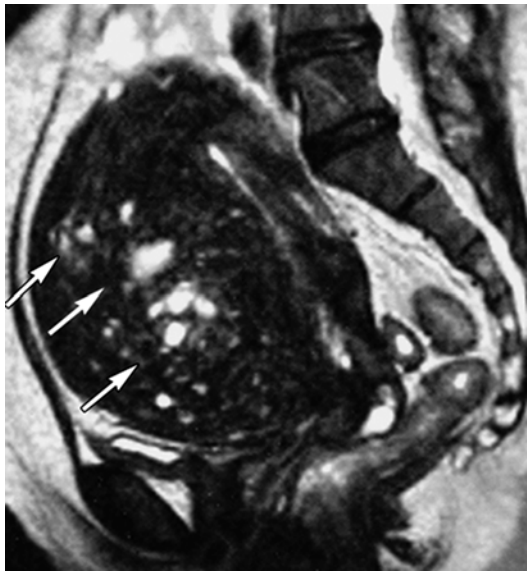

Fig. 8.10 T2 MRI of uterus with focal adenomyosis in the anterior wall (*white arrows*)

fibroid. It has been reported that 28 % of hysterectomy specimens in premenopausal patient contain adenomyosis [50, 51]. Patients with symptomatic adenomyosis have a high risk of hysterectomy and ideally the diagnosis should be made before any minimal invasive therapeutic attempt is undertaken.

No imaging technique can diagnose adenomyosis with absolute certainty. Ultrasound, including elastography and MRI however may demonstrate the different features of the adenomyoma and the fibroid.

The typical features in imaging of the uterine fibroid comprise a homogenous structure with circumscript smooth borders and often a round shape and a distinct vascular capsule, which is visible in power Doppler as well as in elastoscan as a soft rim. The vascularity within the fibroid – not in the capsule – is generally lower than in the myometrium. In contrast, adenomyosis in ultrasound imaging is characterized by ill-defined margins, by heterogeneity with typical hypoechoic striation caused by echogenic foci next to hypoechogenic elements formed by pockets of blood (‘lacunae’) [52, 53]. The shape is often not round but ellipsoid and there is little mass effect on the uterine cavity if any. The lesion is conjunct to the junctional zone that may be variably thickened if diffuse adenomyosis is present. In the coronal plane with 3D ultrasound a higher sensitivity for adenomyosis is reported (cut off level 8 mm) than in the sagittal and transversal plane in 2D ultrasound [54]. The myometrium is asymmetrically thickened [53] or the uterine configuration may be globular. With power Doppler (PD) ultrasound random like vessels are seen in the adenomyotic lesion as in the myometrium but in higher numbers. The use of intracavitary contrast with saline or gel may give more accurate information on the protrusion of the myometrial lesion and support the distinction of adenomyosis and submucous fibroids as the latter tend to protrude more into the cavity [55]. In elastography the amount of pressure applied by the probe affects the brightness and colouring of the acquired images. A steady state image should be obtained to interpret an elastography image. A steady state image of the ute-rus is established when a clear delineation of the serosa is visible. Adenomyosis is in general softer than myometrium, visualized as several bright colours within the dark myometrium (i.e. bright yellow, green or light blue) (Fig. 8.11). While fibroids are clearly delineated, the shape of adenomyosis is irregular. The feasibility of elastography for the discrimination of intrauterine fibroids and adenomyosis, has been reported in literature [29, 56]. There are certain artefacts the examiner has to be aware of. A probe contact artefact is visible in most elastographic images and shows an illuminated area at the point of contact with the ultrasound transducer mimicking softer areas. This bright (yellow) area should not be confused with the presence of adenomyosis. Due to this artefact it is difficult to study the existence of adenomyosis in the low anterior part of the uterus.

In case of excessive pressure or movements of the uterus bright colours will appear in the image defined as movement artefacts. Various bright colours on different locations can be induced even in normal myometrium resembling the appearance of adenomyosis. Both the arcuate plexus and the AV malformations are visible with power and colour Doppler and should not be confused with adenomyosis [28, 56, 57].

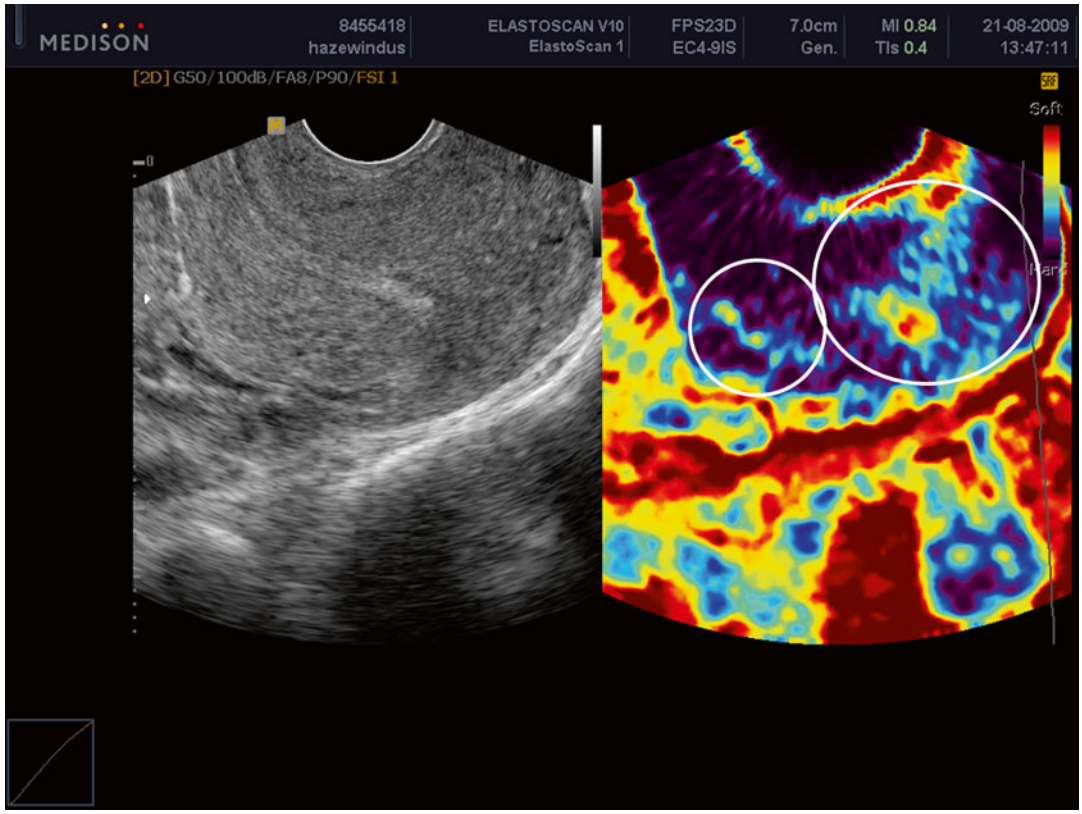

Fig. 8.11 Retroflected uterus with adenomyosis in the anterior wall demonstrated by greyscale and elastography

In those studies that compare transvaginal ultrasound and MRI in the diagnosis of adenomyosis no significant difference in diagnostic accuracy could be demonstrated [58, 59].The sensitivity and specificity are ranging from 70 to 89 % resp. 65 to 98 % in both techniques. The area under the curve (AUC) for the diagnostic performance of MRI in the detection of myomas and adenomyosis is reported 0.81 and 0.73, respectively [57].

Which imaging technique to choose in suspected adenomyosis, ultrasound or MRI, depends on the skills and preference of the clinician. In case of medical treatment (e.g. oral contraception, levonorgestrel releasing IUD) or hysterectomy not the same level of certainty of diagnosis is required as in case of conservative surgical procedures of fibroids. As ultrasound is easier accessible and less costly than MRI this could be the first choice. In doubt a MRI is obligatory.

Size and Volume

On many occasions the fibroid size and volume are essential in determining the therapeutic management. Especially in minimal invasive and often uterus preserving treatments of fibroids, such as laparoscopic myomectomy, hysteroscopic resection or ablation of fibroids, the uterine size and volume are of critical importance regarding ablation and morcellation time and treatment success. The non-perfused volume (NPV) in contrast enhanced MRI or ultrasound of a fibroid is associated with the treatment success of fibroid ablation, being an expression of the non-vital tissue in the fibroid [60]. Finally the response on medical treatment of fibroids, but also its natural course in expectant management may be monitored by serial measurements of size and volume.

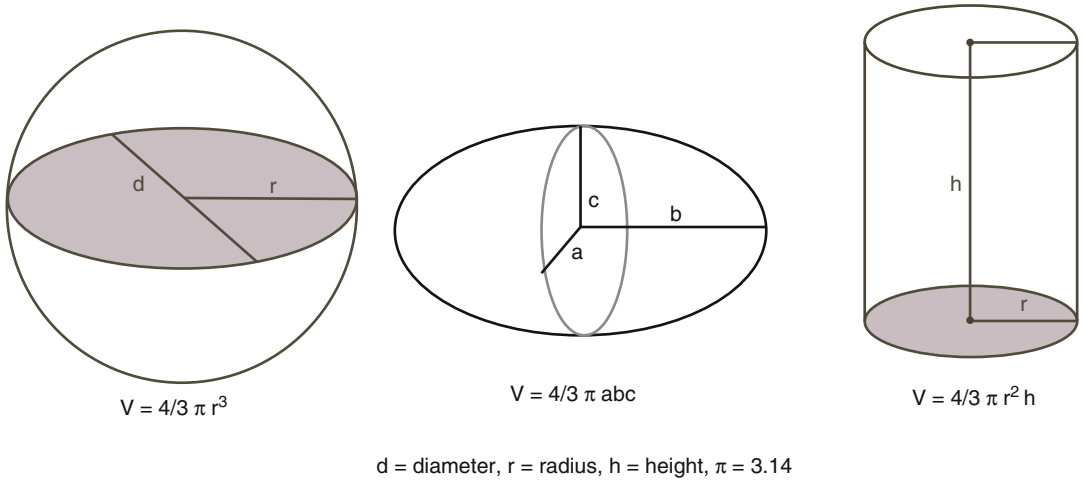

Fig. 8.12 Volume calculations of a sphere, an ellipsoid and a cylinder

Considering the fibroid as a sphere with radius r, its volume is calculated from the size as follows: $4/3*\pi r^3$ (Fig. 8.12). This implies that any increase in size should be raised to the third power calculating the volume as well as the resection or morcellation time. In hysteroscopy, resection time is generally related to distension fluid loss thereby limiting the maximum size of the fibroid suitable for resection. In evaluating treatment options the volume would therefore be the preferable criterion over size alone.

However some fibroids do not have a completely round contour in all planes and seem to be elongated. Therefore the volume calculation of an ellipsoid shape would be more appropriate. The simple but imprecise way of calculating an ellipsoid shape is multiplying the three perpendicular diameters of the structure with 0.5. More precise is the formula $4/3*\pi abc$, where a, b and c are half the diameters in three directions. Sometimes the shape is more similar to a cylinder with radius r and height h, in which case the formula is $\pi*r^2h$. All above mentioned measurements can be made based on 2D images, where diameters in perpendicular planes are measured and used in the respective formulas. With the introduction of stored 3D volumes in MRI and ultrasound more advanced and potentially more reliable methods have become available to measure volumes of structures in the body. Other structures than fibroids may have similar shapes, such as prostate and foetal bladder and have been used also to validate 3D measurement volume techniques. The software of 3D scanning is referred to as virtual organ computer-aided analysis (VOCAL). It enables the examiner to evaluate 3D stored image volumes and to calculate volumes. After defining the round shape (sphere) with two callipers the software computes the sphere volume, but also the volume of more ellipsoid shapes referred to in the software as 'prostate' or 'solid' can be computed (Fig. 8.13). Finally the software provides the possibility to manually depict the structure in 6–12 radial planes [61] or in parallel planes. This so called planimetric method calculates the sum of the multiple areas multiplied by the thickness of each individual slice or sector and is particularly suitable for irregular structures such as non-perfused areas in an ablated fibroid.

In the reliability (reproducibility), mean standard error and deviation are used as outcome, while in the validation studies the volume measurements are generally compared to the volume reference test by water displacement, in history described by Archimedes [62]. In ultrasound the planimetric calculations are considered more time consuming but also more precise than the sphere or ellipsoid estimates [60, 62, 63]. In MRI different opinions are reported on the pref-

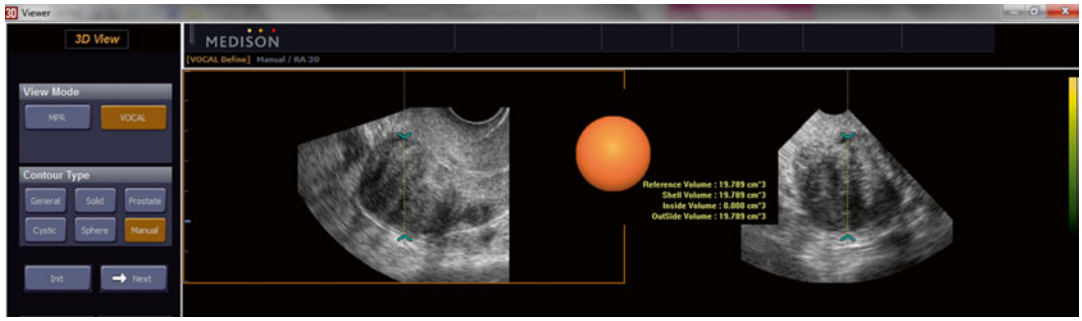

Fig. 8.13 Screenshot in Sonoview Pro of automatic volume calculation of a sphere using VOCAL

erence of on the one hand ellipsoid volume measurement [64] and of on the other hand planimetry [63].

Classification

Besides from its volume and shape the fibroid may be defined according to its topography in the uterus (anterior, fundal, posterior) and its position in the myometrium. Classifying tumors means to attribute characteristics in a standardised way in order to distinguish tumors of different behaviour and clinical outcome. So it is generally assumed that fibroids that are indenting the uterine cavity cause more symptoms of abnormal uterine bleeding than subserous fibroids, though this assumption is waiting to be confirmed in clinical research [65].

After the introduction of hysteroscopic resection there was need for a submucous fibroid classification that could predict outcome in terms of complete resection as this was predominantly associated with relief of heavy menstrual bleeding. The proposed classification by Wamsteker et al. defined fibroids according to their myometrial extension: type 0 no extension, type 1 < 50 % extension, type 2 ≥ 50 % extension in the myometrium and was related to the probability of complete resection [6, 7]. This classification was adopted by the European society of hysteroscopy and later, after its merging with the club Raoul Palmere, by the European Society of Gynaecological Endoscopy (ESGE). The relationship between class and complete resection could not be confirmed by Lasmar et al. [66] who proposed a modified classification incorporating also parameters as the distance of the base of the fibroid from the uterine wall, the size of the fibroid (cm), and the topography of the fibroid in the uterine cavity. They reported a relationship between class not only with complete resection but also with operating time and distension fluid loss. This classification was not adopted by a professional organisation which ultimately limits its significance as a classification only enables multicentric comparison if widely implemented.

For the same reason after introduction of the fibroid ablation techniques and the uterine artery embolisation as treatment for symptomatic fibroids, the need arose for a classification of intramural and subserous fibroids. Better counselling on treatment options should be possible if fibroids could be classified according to characteristics that predicted treatment effect. Munro et al. [8] described the PALM-COEIN classification of patient characteristics in case of abnormal uterine bleeding. PALM-COEIN stands for 'polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not yet classified'. This classification system has been approved by the International Federation of Gynecology and Obstetrics (FIGO) Executive Board as a FIGO classification system. The leiomyoma part of the PALM-COEIN classification adds to the submucous fibroid classification (type 0, 1, 2) intramural (type 3, 4, 5, 2–5) and subserous fibroid types (type 6, 7). Type 2–5 is protruding in the uterine aswell as in the abdominal cavity and type 7 is pedunculated (Fig. 8.14). The

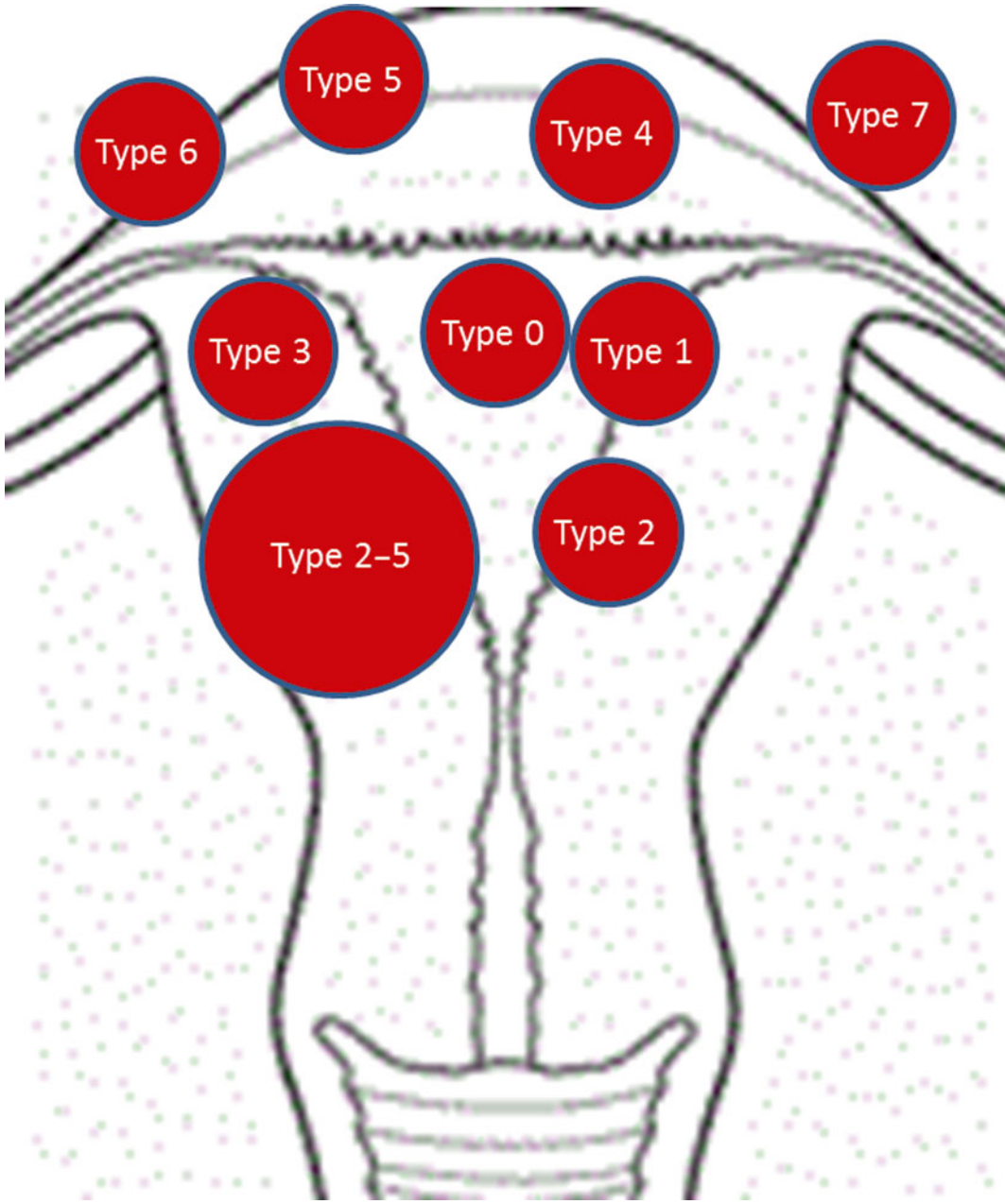

Fig. 8.14 FIGO classification of uterine fibroids [8]

standard for classification of submucous fibroids by MRI or by transvaginal ultrasound of the uterus, using contrast in the cavity, the saline of gel infusion sonography (SIS or GIS). The reliability of MRI has been reported higher than the ultrasound techniques which on the other hand is more easily accessible, generally performed by the gynaecologist and has low costs [67].

Vascularity

The vascularity of vital fibroids has a characteristic pattern: within the fibroids a low vessel count, while around the fibroid vessels are abundantly present. These vessels can be seen in Doppler examination, but also in hysteroscopy in the overlying endometrium preceding submu-

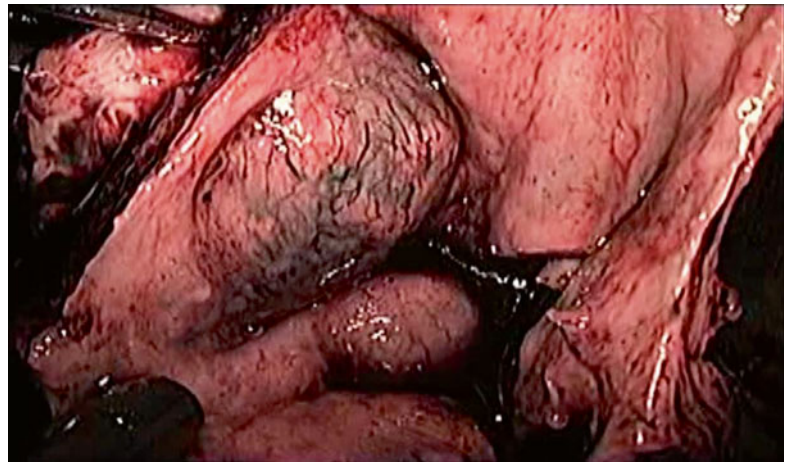

Fig. 8.15 Submucous fibroid in uterine cavity in uterus specimen examined by narrow band imaging (NBI). The vascularity of the fibroid overlying endometrium is prominent

cous fibroid resection (Fig. 8.15). It is hypothesized that within the fibroid antiangiogenic factors inhibit the neovascularisation. Due to the hypoxic environment directly outside the fibroid VEGF and other angiogenic stimuli promote vessel formation thus creating the 'vascular capsule' [68]. It is well known that fibroids that have undergone hyaline degeneration are less vascularized than non-degenerated fibroids [69], implying that the assessment of fibroid vascularisation may predict the natural course of the fibroid. Also the degeneration induced by uterine artery embolization reduces, as might be expected, signal intensity in contrast enhanced MRI, an expression of vascularity [69]. The typical vessel pattern of fibroids can be distinguished from the vessel pattern in adenomyosis, which shows, apart from greyscale differences (see above) a random like vessel pattern in the lesion and lacking the boundaries so clearly depicted by the vascular capsule in fibroids. In leiomyosarcoma, sarcoma most likely to be confused with fibroids, the vascularity has been increased, while the vessels have lower resistance and pulsatility index (RI and PI) and the blood flow has a higher peak than in fibroids [40]. Finally the vascularity of the fibroid is associated with responsiveness of the fibroid to embolization [70] and ablation by ultrasound or radiofrequency [71]. Uterine artery embolization offers low benefit in fibroids that already have little blood supply, while fibroid ablation offers low treatment benefit in patients with highly vascularized fibroids as they conduct the thermal energy before a critical temperature has reached that is required to destroy the tissue.

How to Assess Fibroid Vascularity with 3DPD?

After positioning the 3D US probe the area of interest is visualized, the power Doppler function is activated, the size of the sector in adjusted and the gain is set higher until artefact scatter is seen and then slightly set lower in order to have optimal sensitivity. The 3D US is activated and the scanning angle determined depending on the size of the fibroid. The largest diameter of the fibroid is in the scanning plane and while making the automated sweep, the transducer is hold still. The acquired volume can be examined on the ultrasound machine wither on a PC with special software provided by the manufacturer of the US machine. With the help of the software an area of interest can be selected (VOCAL), the volume measured and the vascular properties (VI, FI and VFI) produced with the function 'histogram' (Fig. 8.16). Obviously incorporating the vascular capsule in the histogram will change the vascularity of the fibroid substantially. Therefore it is recommended to estimate the vascularity of the fibroid first and then extending the histogram with the area of interest just outside the fibroid. A

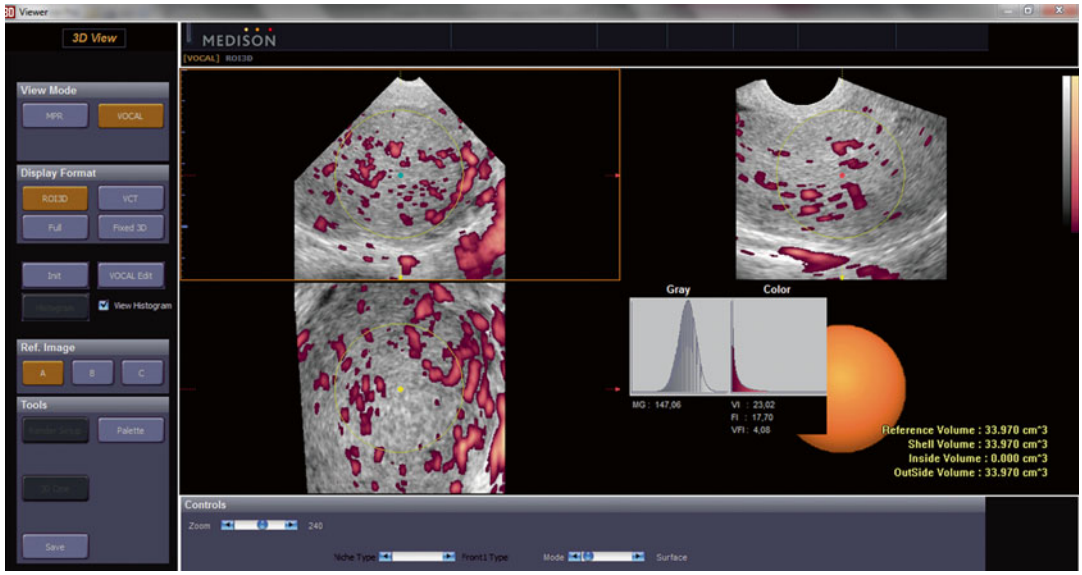

Fig. 8.16 Screenshot of Sonoview Pro showing a histogram in a selected volume with vascular index, flow index and vascular flow index

shell around the fibroid can automatically defined in the software and the histogram created. A pitfall is to have the uterine vessels erroneously in the shell histogram. Despite these shortcomings the reproducibility between sonographers seems to be good.

Conclusions

The objective of imaging is to visualize otherwise hidden structures in the body in order to – by better diagnosis and topography – optimize treatment. In preparing surgery, imaging can make treatment more selective with less collateral damage, e.g. ablation or resection, and therewith contributes to the everlasting obligation to harm as little as possible. MRI, 2D real time transabdominal and transvaginal ultrasound and possibly PET-scans are well established in fibroid diagnosis, whereas X-ray and CT play no significant role. Recent developments such as 3D ultrasound and 3D power Doppler may have a role in distinction of the fibroid from adenomyosis and leiomyosarcoma and prediction of conservative fibroid treatment but need further confirmation in future clinical research.

References

1. Popp LW, Gaetje R, Stoyanov M. Accuracy of bimanual palpation versus vaginosonography in determination of the measurements of pelvic tumors. Arch Gynecol Obstet. 1993;252(4):197–202.
2. Harb TS, Adam RA. Predicting uterine weight before hysterectomy: ultrasound measurements versus clinical assessment. Am J Obstet Gynecol. 2005;193(6):2122–5.
3. Kho KA, Nezhat CH. Evaluating the risks of electric uterine morcellation. JAMA. 2014;10.
4. Falcone T, Parker WH. Surgical management of leiomyomas for fertility or uterine preservation. Obstet Gynecol. 2013;121(4):856–68.
5. Miller CE. Unmet therapeutic needs for uterine myomas. J Minim Invasive Gynecol. 2009;16(1):11–21.
6. Wamsteker K, de Blok S. Diagnostic hysteroscopy: technique and documentation. In: Sutton CJG, Diamond M, editors. Endoscopic surgery for gynaecologists. London: WB Saunders; 1993. p. 263–76.
7. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstet Gynecol. 1993;82(5):736–40.
8. Munro MG, Critchley HO, Broder MS, Fraser IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011;113(1):3–13.
9. Hurley V. Imaging techniques for fibroid detection. Baillieres Clin Obstet Gynaecol. 1998;12(2):213–24.

10. Casillas J, Joseph RC, Guerra Jr JJ. CT appearance of uterine leiomyomas. Radiographics. 1990;10(6): 999–1007.
11. Dueholm M, Lundorf E, Sorensen JS, Ledertoug S, Olesen F, Laursen H. Reproducibility of evaluation of the uterus by transvaginal sonography, hysterosonographic examination, hysteroscopy and magnetic resonance imaging. Hum Reprod. 2002;17(1):195–200.
12. Bega G, Lev-Toaff A, Kuhlman K, Kurtz A, Goldberg B, Wapner R. Three-dimensional ultrasonographic imaging in obstetrics: present and future applications. J Ultrasound Med 2001; 20(4):391–408.
13. Lee C, Salim R, Ofili-Yebovi D, Yazbek J, Davies A, Jurkovic D. Reproducibility of the measurement of submucous fibroid protrusion into the uterine cavity using three-dimensional saline contrast sonohysterography. Ultrasound Obstet Gynecol. 2006;28(6): 837–41.
14. de Kroon CD, Louwe LA, Trimbos JB, Jansen FW. The clinical value of 3-dimensional saline infusion sonography in addition to 2-dimensional saline infusion sonography in women with abnormal uterine bleeding: work in progress. J Ultrasound Med. 2004; 23(11):1433–40.
15. Leone FP, Bignardi T, Marciante C, Ferrazzi E. Sonohysterography in the preoperative grading of submucous myomas: considerations on three-dimensional methodology. Ultrasound Obstet Gynecol. 2007;29(6):717–8.
16. Pairleitner H, Steiner H, Hasenoehrl G, Staudach A. Three-dimensional power Doppler sonography: imaging and quantifying blood flow and vascularization. Ultrasound Obstet Gynecol. 1999;14(2):139–43.
17. Kim SH, Lee JM, Kim YJ, Lee JY, Han JK, Choi BI. High-definition flow Doppler ultrasonographic technique to assess hepatic vasculature compared with color or power Doppler ultrasonography: preliminary experience. J Ultrasound Med. 2008;27(10):1491–501.
18. Alcazar JL, Kudla MJ. Three-dimensional vascular indices calculated using conventional power Doppler and high-definition flow imaging: are there differences? J Ultrasound Med. 2010;29(5):761–6.
19. de Kroon CD, de Bock GH, Dieben SW, Jansen FW. Saline contrast hysterosonography in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG. 2003;110(10):938–47.
20. De Vries LD, Dijkhuizen FP, Mol BW, Brolmann HA, Moret E, Heintz AP. Comparison of transvaginal sonography, saline infusion sonography, and hysteroscopy in premenopausal women with abnormal uterine bleeding. J Clin Ultrasound. 2000;28(5): 217–23.
21. Bij de Vaate AJ, Brolmann HA, van der Slikke JW, Emanuel MH, Huirne JA. Gel instillation sonohysterography (GIS) and saline contrast sonohysterography (SCSH): comparison of two diagnostic techniques. Ultrasound Obstet Gynecol. 2010;35(4): 486–9.
22. Ayoubi JM, Fanchin R, Ferretti G, Pons JC, Bricault I. Three-dimensional ultrasonographic reconstruction of the uterine cavity: toward virtual hysteroscopy? Eur Radiol. 2002;12(8):2030–3.
23. Quaia E. Assessment of tissue perfusion by contrast-enhanced ultrasound. Eur Radiol. 2011;21(3): 604–15.
24. Wang F, Zhang J, Han ZY, Cheng ZG, Zhou HY, Feng L, et al. Imaging manifestation of conventional and contrast-enhanced ultrasonography in percutaneous microwave ablation for the treatment of uterine fibroids. Eur J Radiol. 2012;81(11):2947–52.
25. Dorenberg EJ, Hol PK, Jakobsen JA, Ring E. Improved infarction rates in fibroids after the introduction of contrast-enhanced ultrasound during uterine artery embolization. Acta Radiol. 2012;53(1):34–8.
26. Zhang XL, Zheng RQ, Yang YB, Huang DM, Song Q, Mao YJ, et al. The use of contrast-enhanced ultrasound in uterine leiomyomas. Chin Med J (Engl). 2010;123(21):3095–9.
27. Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. Ultrason Imaging. 1991;13(2):111–34.
28. Stoelinga B, Hehenkamp WJ, Brolmann HA, Huirne JA. Real-time elastography for assessment of uterine disorders. Ultrasound Obstet Gynecol. 2014;43(2):218–26.
29. Ami O, Lamazou F, Mabille M, Levaillant JM, Deffieux X, Frydman R, et al. Real-time transvaginal elastosonography of uterine fibroids. Ultrasound Obstet Gynecol. 2009;34(4):486–8.
30. Berger A. Magnetic resonance imaging. BMJ. 2002;324(7328):35.
31. Kitajima K, Murakami K, Kaji Y, Sugimura K. Spectrum of FDG PET/CT findings of uterine tumors. AJR Am J Roentgenol. 2010;195(3):737–43.
32. Yanai H, Wani Y, Notohara K, Takada S, Yoshino T. Uterine leiomyosarcoma arising in leiomyoma: clinicopathological study of four cases and literature review. Pathol Int. 2010;60(7):506–9.
33. Leibsohn S, d'Ablaing G, Mishell Jr DR, Schlaerth JB. Leiomyosarcoma in a series of hysterectomies performed for presumed uterine leiomyomas. Am J Obstet Gynecol. 1990;162:968–74; discussion 968–74.
34. Schwartz LB, Diamond MP, Schwartz PE. Leiomyosarcomas: clinical presentation. Am J Obstet Gynecol. 1993;168(180–183):180–3.
35. Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol. 1994; 83(414–418):414–8.
36. Seidman MA, Oduyebo T, Muto MG, Crum CP, Nucci MR, Quade BJ. Peritoneal dissemination complicating morcellation of uterine mesenchymal neoplasms. PLoS One. 2012;7(11):e50058.
37. Seki K, Hoshihara T, Nagata I. Leiomyosarcoma of the uterus: ultrasonography and serum lactate dehydrogenase level. Gynecol Obstet Invest. 1992;33(2): 114–8.
38. Evans HL, Chawla SP, Simpson C, Finn KP. Smooth muscle neoplasms of the uterus other than ordinary

leiomyoma. A study of 46 cases, with emphasis on diagnostic criteria and prognostic factors. Cancer. 1988;62(2239–2247):2239–47.
39. Botsis D, Kassanos D, Antoniou G, Pyrgiotis E, Karakitsos P, Kalogirou D. Adenomyoma and leiomyoma: differential diagnosis with transvaginal sonography. J Clin Ultrasound. 1998;26(1):21–5.
40. Szabo I, Szantho A, Csabay L, Csapo Z, Szirmai K, Papp Z. Color Doppler ultrasonography in the differentiation of uterine sarcomas from uterine leiomyomas. Eur J Gynaecol Oncol. 2002;23(1): 29–34.
41. Exacoustos C, Romanini ME, Amadio A, Amoroso C, Szabolcs B, Zupi E, et al. Can gray-scale and color Doppler sonography differentiate between uterine leiomyosarcoma and leiomyoma? J Clin Ultrasound. 2007;35(8):449–57.
42. Minsart AF, Ntoutoume SF, Vandenhoute K, Jani J, Van PC. Does three-dimensional power Doppler ultrasound predict histopathological findings of uterine fibroids? A preliminary study. Ultrasound Obstet Gynecol. 2012;40(6):714–20.
43. Tanaka YO, Nishida M, Tsunoda H, Okamoto Y, Yoshikawa H. Smooth muscle tumors of uncertain malignant potential and leiomyosarcomas of the uterus: MR findings. J Magn Reson Imaging. 2004;20(6):998–1007.
44. Lerman H, Bar-On S, Helpman L, Even-Sapir E, Grisaru D. Estrogen-dependent variations in 18 F-fluorodeoxyglucose uptake in uterine leiomyomas. Int J Gynecol Cancer. 2012;22(7):1187–91.
45. Umesaki N, Tanaka T, Miyama M, Kawamura N, Ogita S, Kawabe J, et al. Positron emission tomography with (18)F-fluorodeoxyglucose of uterine sarcoma: a comparison with magnetic resonance imaging and power Doppler imaging. Gynecol Oncol. 2001;80(3):372–7.
46. Yoshida Y, Kiyono Y, Tsujikawa T, Kurokawa T, Okazawa H, Kotsuji F. Additional value of 16alpha-[18 F]fluoro-17beta-oestradiol PET for differential diagnosis between uterine sarcoma and leiomyoma in patients with positive or equivocal findings on [18 F] fluorodeoxyglucose PET. Eur J Nucl Med Mol Imaging. 2011;38(10):1824–31.
47. Zhao Z, Yoshida Y, Kurokawa T, Kiyono Y, Mori T, Okazawa H. 18 F-FES and 18 F-FDG PET for differential diagnosis and quantitative evaluation of mesenchymal uterine tumors: correlation with immunohistochemical analysis. J Nucl Med. 2013; 54(4):499–506.
48. Bell SW, Kempson RL, Hendrickson MR. Problematic uterine smooth muscle neoplasms. A clinicopathologic study of 213 cases. Am J Surg Pathol. 1994;18(6):535–58.
49. Kawamura N, Ichimura T, Ito F, Shibata S, Takahashi K, Tsujimura A, et al. Transcervical needle biopsy for the differential diagnosis between uterine sarcoma and leiomyoma. Cancer. 2002;94(6):1713–20.
50. Vercellini P, Parazzini F, Oldani S, Panazza S, Bramante T, Crosignani PG. Adenomyosis at hysterectomy: a study on frequency distribution and patient characteristics. Hum Reprod. 1995;10(5):1160–2.
51. Vercellini P, Cortesi I, De GO, Merlo D, Carinelli SG, Crosignani PG. Transvaginal ultrasonography versus uterine needle biopsy in the diagnosis of diffuse adenomyosis. Hum Reprod. 1998;13(1O):2884–7.
52. Huang RT, Chou CY, Chang CH, Yu CH, Huang SC, Yao BL. Differentiation between adenomyoma and leiomyoma with transvaginal ultrasonography. Ultrasound Obstet Gynecol. 1995;5(1):47–50.
53. Atri M, Reinhold C, Mehio AR, Chapman WB, Bret PM. Adenomyosis: US features with histologic correlation in an in-vitro study. Radiology. 2000; 215(3):783–90.
54. Exacoustos C, Brienza L, Di GA, Szabolcs B, Romanini ME, Zupi E, et al. Adenomyosis: three-dimensional sonographic findings of the junctional zone and correlation with histology. Ultrasound Obstet Gynecol. 2011;37(4):471–9.
55. Alborzi S, Parsanezhad ME, Mahmoodian N, Alborzi S, Alborzi M. Sonohysterography versus transvaginal sonography for screening of patients with abnormal uterine bleeding. Int J Gynaecol Obstet. 2007;96(1):20–3.
56. Tessarolo M, Bonino L, Camanni M, Deltetto F. Elastosonography: a possible new tool for diagnosis of adenomyosis? Eur Radiol. 2011;21(7):1546–52.
57. Stamatopoulos CP, Mikos T, Grimbizis GF, Dimitriadis AS, Efstratiou I, Stamatopoulos P, et al. Value of magnetic resonance imaging in diagnosis of adenomyosis and myomas of the uterus. J Minim Invasive Gynecol. 2012;19(5):620–6.
58. Reinhold C, Tafazoli F, Mehio A, Wang L, Atri M, Siegelman ES, et al. Uterine adenomyosis: endovaginal US and MR imaging features with histopathologic correlation. Radiographics. 1999;19 Spec No:S147–60.
59. Bazot M, Cortez A, Darai E, Rouger J, Chopier J, Antoine JM, et al. Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis: correlation with histopathology. Hum Reprod. 2001;16(11):2427–33.
60. Quinn SD, Vedelago J, Kashef E, Gedroyc W, Regan L. Measurement of uterine fibroid volume: a comparative accuracy and validation of methods study. Eur J Obstet Gynecol Reprod Biol. 2013;171(1):161–5.
61. Bordes A, Bory AM, Benchaib M, Rudigoz RC, Salle B. Reproducibility of transvaginal three-dimensional endometrial volume measurements with virtual organ computer-aided analysis (VOCAL) during ovarian stimulation. Ultrasound Obstet Gynecol. 2002;19(1):76–80.
62. Farrell T, Leslie JR, Chien PF, Agustsson P. The reliability and validity of three dimensional ultrasound volumetric measurements using an in vitro balloon and in vivo uterine model. BJOG. 2001;108(6):573–82.
63. Joe BN, Suh J, Hildebolt CF, Hovsepian DM, Johnston B, Bae KT. MR volumetric measurements of the myomatous uterus: improved reliability of stereology over linear measurements. Acad Radiol. 2007; 14(4):455–62.

64. Broekmans FJ, Heitbrink MA, Hompes PG, Schoute E, Falke T, Schoemaker J. Quantitative MRI of uterine leiomyomas during triptorelin treatment: reproducibility of volume assessment and predictability of treatment response. Magn Reson Imaging. 1996;14(10):1127–35.
65. Wegienka G, Baird DD, Hertz-Picciotto I, Harlow SD, Steege JF, Hill MC, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol. 2003;101(3):431–7.
66. Lasmar RB, Barrozo PR, Dias R, Oliveira MA. Submucous myomas: a new presurgical classification to evaluate the viability of hysteroscopic surgical treatment–preliminary report. J Minim Invasive Gynecol. 2005;12(4):308–11.
67. Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Evaluation of the uterine cavity with magnetic resonance imaging, transvaginal sonography, hysterosonographic examination, and diagnostic hysteroscopy. Fertil Steril. 2001;76(2):350–7.
68. Weston G, Vollenhoven B, Rogers PAW. Angiogenesis and vascular responses in leiomyomata. In: Brosens I, editor. Uterine leiomyomata; pathogenesis and management. London: Taylor & Francis; 2006. p. 67–82.
69. Shimada K, Ohashi I, Kasahara I, Miyasaka N, Shibuya H. Triple-phase dynamic MRI of intratumoral vessel density and hyalinization grade in uterine leiomyomas. AJR Am J Roentgenol. 2004;182(4):1043–50.
70. Isonishi S, Coleman RL, Hirama M, Iida Y, Kitai S, Nagase M, et al. Analysis of prognostic factors for patients with leiomyoma treated with uterine arterial embolization. Am J Obstet Gynecol. 2008;198(3):270–6.
71. Funaki K, Fukunishi H, Funaki T, Sawada K, Kaji Y, Maruo T. Magnetic resonance-guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted magnetic resonance images. Am J Obstet Gynecol. 2007;196(2):184–6.
72. Carrafiello G, Recaldini C, Fontana F, Ghezzi F, Cuffari S, Lagana D, et al. Ultrasound-guided radiofrequency thermal ablation of uterine fibroids: medium-term follow-up. Cardiovasc Intervent Radiol. 2010;33(1):113–9.

Hysteroscopic Myomectomy

9

Sergio Haimovich, Marina Eliseeva,
and Ospan A. Mynbaev

Introduction

Bozzini is the first scientist who applied light to visualize insight of the human body in 1805. Then Desormeaux introduced his devise for cystoscopy and he used the term 'endoscopie' in 1853 (Fig. 9.1).

Pantealoni performed the first investigation of uterine cavity in a 60-year-old woman with abnormal uterine bleeding by means of Desormeaux's device in 1869. He could see an endometrial polyp and cauterized it with silver nitrate under endoscopic view. He was the first who used both diagnostic and treatment abilities of this approach, which can be considered as the beginning of the principle "see and treat" by direct visual control of uterine cavity.

It was obvious that visualization of the uterine cavity is an important tool for the diagnosis of endometrial pathology with enabling a new treatment choice. Therefore many researchers were interested in improvement of uterine cavity visualization. Achievements of the state of the art, including principles of optics, fiberoptics, Hopkins telescope, television, electricity, light, light sources, video and other technologies (Fig. 9.2) were step by step implemented to design modern hysteroscopic equipment (Fig. 9.3 and Table 9.1).

Hamou's hysteroscope was designed with an improved 4-mm rod lens system scope visual optics inserted into a diagnostic sheath to guide the distension media into the uterine cavity. Microcolpohysteroscope designed by Hamou revolutionized the hysteroscopy technique (Fig. 9.4), therefore according to his deserts in this field Hamou is considered as the father of modern hysteroscopy (Fig. 9.5).

In turn, new advances in development of distension medium are based on principles of fluids diffusion and electrolytic conduction (Table 9.2). So, uterine cavity distention and illumination was also improved by irrigation with continuous flow (Heineberg 1914; Seymour 1926) and application of CO_2 (Rubin 1925) and liquid media (Creevy and Webb 1947; Edstrom and Fernstrom 1970).

S. Haimovich, MD (✉)
Hysteroscopy Unit, Del Mar University Hospital, Barcelona, Spain
e-mail: Sergio@haimovich.net

M. Eliseeva, MD, PhD
Peoples' Friendship University of Russia, Moscow, Russia

Russian-German Center of Reproduction and Clinical Embryology, "Generation NEXT", Moscow, Russia

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia
e-mail: marinaeliseeva@hotmail.com

O.A. Mynbaev, MD, MSc, PhD, ScD
Peoples' Friendship University of Russia, Moscow, Russia

International Translational Medicine and Biomodelling Research Group, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia

Moscow State University of Medicine and Dentistry, Moscow, Russia
e-mail: ospanmynbaev@crec.mipt.ru; ospanmynbaev@hotmail.com

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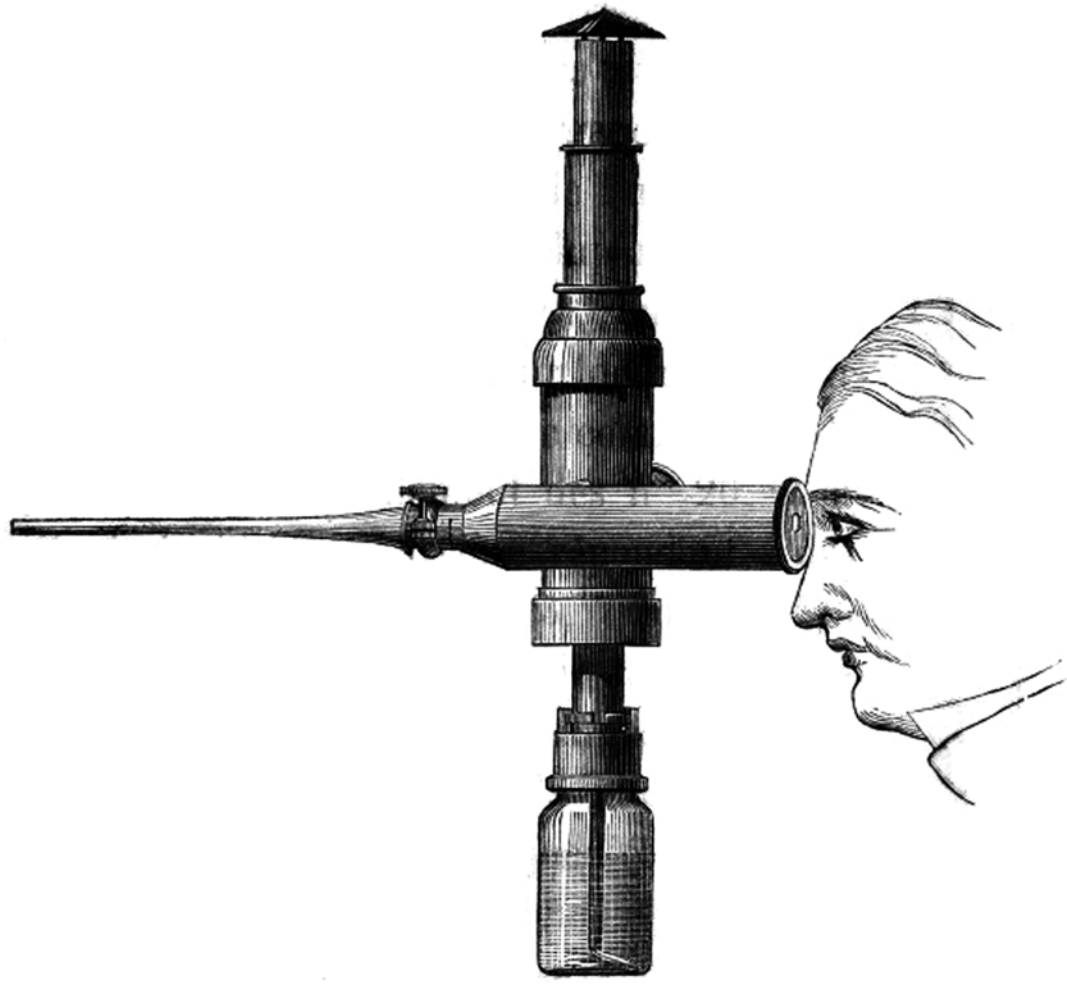

Fig. 9.1 The Desormeaux's endoscope (Courtesy of the Wellcome Library, London. Published under the Creative Commons Attribution)

All developments of technologies have allowed to design modern hysteroscopic tool according to Valle and Sciarra [1], which consists of 'a telescope 2–4 mm in diameter, with Foroblique vision; a metallic sheath for the telescope and accessory channels to deliver the distending medium and introduce operating instruments; a connecting bridge with special channels to introduce manipulating instruments; a cold light fiberoptic bundle to transmit the light; an external light source for illumination; and when electrocoagulation is to be used, an appropriate electrosurgical source´.

Most modern hysteroscopic procedures have developed in 1980s when new generation of miniaturized hysteroscopes was designed owing to Hopkins telescopic principles. Subsequently office hysteroscopies were mostly performed as the first diagnostic step to evaluate intrauterine pathologies and only easy procedures such as biopsy, polypectomy and adhesiolysis, were done by this approach at outpatient clinics. Further hysteroscopic surgical procedures have performed as the second step mostly by monopolar coagulation and mechanical instruments under anesthesia and dilatation of cervix at inpatient clinics in the operation theatre till 1997. Mechanical instruments were used mostly to remove polyps, adhesiolysis and for biopsy, whereas resectoscope was

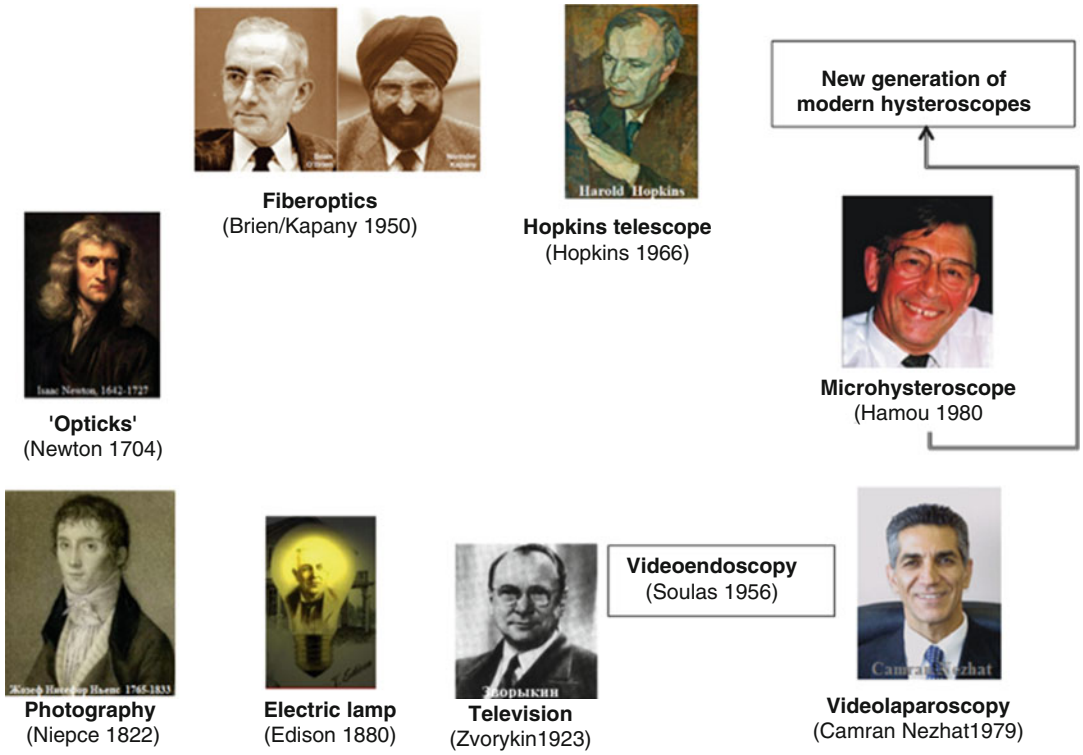

Fig. 9.2 Principles of basic sciences and technologies applied for a design of hysteroscopic tools

Fig. 9.3 Optical principles of modern hysteroscopic technique

Table 9.1 Principles of hysteroscopic equipment design

Purposes	Developed tools
Delivery	Tubus or sheath
Visualization	Optics/telescope, camera and screen
Illumination	Light source and optical fiber (light guide)
Distension	Distension medium (CO_2 or liquid) and additional in/out flow channels
Surgical	Manipulation channel, mechanical and electrical instruments, lasers

the main surgical tool for myomectomy and resection of uterine septum.

Introduction of bipolar system 'Gynecare Versa Point' by Ethicon Inc. in 1997 was the turning point of modern office hysteroscopy. This technology enabled to increase spectrum of intrauterine surgical procedures by means of thin miniaturized instruments without both anesthesia and dilatation of cervix at outpatient clinics.

Submucous Myoma

Submucous myoma (SMM) is a potentially dangerous pathology for women's health with undesirable consequences. Therefore a hysteroscopic management of SMM represented a challenge in our practice since in the past hysterectomy was the only reliable surgical option of this pathology.

The first hysteroscopic myomectomy was performed by Robert Neuwirth, from Mount Sinai Hospital in NY in 1976, using an urologic resectoscope and he developed resectoscopic surgery of SMMs.

Since then many hysteroscopic procedures have replaced old, invasive techniques, such as dilatation, curetaje and even hysterectomy. Nowadays by means of advanced bipolar instruments and other alternatives such as laser and morsellation with miniaturized instruments we have modern office hysteroscopy, which has begun to completely replacing more invasive operating-room procedures.

In the last decades we have witness many developments in the surgical management of this SMM, with an increase in our efficacy to solve the problem by a minimally invasive way. Today we have better and thinner optical hysteroscopes, with more sophisticated system of lenses and prisms to give the operator a well-illuminated image, with excellent contrast and resolution. Although resectoscopy in theater is still the prevalent technique for myomectomy, in the last 20 years huge advances were made in the use of diagnostic hysteroscopes for treatment purposes with an outpatient on a "see and treat" principle.

The advantages of outpatient operative hysteroscopy include the possibility to diagnose and treat intrauterine lesions in a single session and the convenience and efficiency for both the physician and patient. An additional benefit of office-based operative hysteroscopy has been suggested by Lindheim et al. [2], who more than a decade ago, noted the cost saving per case of at least 50 % when compared with the hospital equivalent. The approach with vaginoscopy or "no touch" technique, without using speculum, tenaculum or even anesthesia is another well tolerated advantage of office hysteroscopy and patients reported just little discomfort [3].

Fig. 9.4 Hamou's microcolpohysteroscope

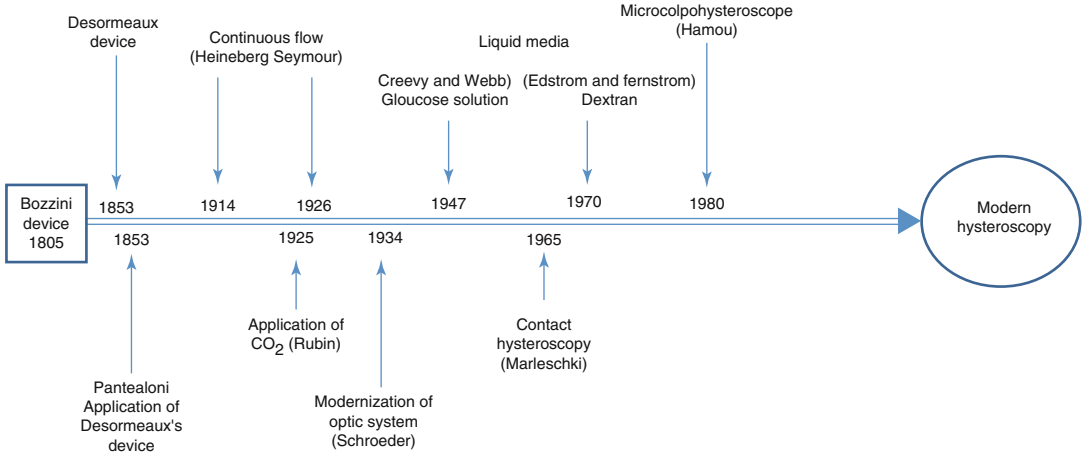

Fig. 9.5 History of the development of hysteroscopy

Table 9.2 Development steps of hysteroscopic equipment and distention media

Optics/telescope	Distension channel and media	Modern distention media
Desormeaux's endoscope (Desormeaux 1853)	Aspiration and irrigation channel (Heineberg 1914; Seymour 1926);	Isotonic ionic solutions;
Photo endoscopy/cystoscopy (Nitze 1877)	CO_2 – for distention (Rubin 1925);	Ringer's Lactate;
Modernization of optic system (Schroeder 1934)	Glucose solution – as a distention media (Creevy and Webb, 1947);	5 % dextrose in water;
Contact hysteroscopy (Marleschki 1965)	Dextran (Edstrom and Fernstrom 1970)	1.5 % glycine, sorbitol, cytal;
Microcolpohysteroscope (Hamou 1980)		Hyskon (32 % dextran 70)

Indications for Myomectomy

Any woman with symptomatic SMM is a candidate for hysteroscopic myomectomy. SMMs are represented only 5–10 % of all the myomas but in many cases are associated to symptoms such as heavy menstrual bleeding (HMB), infertility and recurrent pregnancy lost. [4, 5] Less frequent reported indications include dysmenorrhea [6], aspecific pelvic pain [7]. It is well known that HMB is related with SMM is not capable of being cured by conventional treatment ways [8]. A classic theory, first suggested by Sampson in 1912 (*Surg Gynecol Obstet*, 14:215–230), states that local dysregulation of the vascular structures in the uterus is responsible for this abnormal bleeding. Today we know that in addition to endometrial and uterine cavity local structure alterations due to growing SMM, several signaling pathways initiated by growth and angiogenic factors are involved in this process.

Infertile patients with fibroids that impinge upon the endometrial cavity have poorer reproductive outcomes than a population of infertile patients without fibroids and that removal of fibroids with a pathologic intracavitary component seems to be of benefit [9]. Therefore radical treatment choice by hysterectomy has considered as the main standard of surgical treatment for symptomatic submucous fibroids.

Advances of hysteroscopic technique and introduction of presurgical treatment to decrease size of fibroids have dramatically changed management strategy of submucous myomas.

Classifications of Submucous Myomas

A systematic classification of submucous myomas is necessary in order to standardize hysteroscopic diagnostic and treatment management as well as for a comparative analysis of results in research reports. Such parameters of myomas as their penetration into myometrium (sessile), localization in the uterine cavity and size are critical determinants of their clinical manifestation and for the treatment strategy. Expert teams of many international societies including European Society of Hysteroscopy (ESH), European Society for Gynaecological Endoscopy (ESGE) and American Association of Gynecologic Laparoscopists (AAGL) the International Federation of Gynecology and Obstetrics (FIGO) have developed classification systems to implement them with their guidelines concerning management of patients with myomas.

The most known and widely cited classification system of submucous myomas was proposed by Wamsteker et al. (1993) according to degree of intramural extension of sessile fibroids. Further this system named the Wamsteker classification has been adopted by many societies such as ESH in 1993, ESGE in 2003 and AAGL in 2012, FIGO in 2011 to a certain extent variations. This system is included three types of myomas. Pedunculated myomas entirely within endometrial cavity without myometrial extension are classified as type 0 fibroids. Sessile fibroids with intramural extension less than 50 % and with angle of myoma surface to uterine wall less than 90-degree are classified as type II fibroids,

whereas intramural extension more than 50 % and angle of myoma surface to uterine wall more than 90-degree – as type II fibroids [10, 11].

FIGO working group on menstrual disorders introduced "Classification system including leiomyoma sub classification system" with modified the Wamsteker classification [12]. However this sophisticated classification system is difficult to apply for clinicians since the main purpose of this working group was the causes of abnormal uterine bleeding in nongravid women of reproductive age.

Further Lasmar et al. [13] introduced a classification system by incorporating four main parameters such as:

1. The largest myoma diameter
2. Extension of fibroid base to endometrial cavity surface
3. Penetration of fibroid into myometrium
4. Fibroid location along the uterine wall.

These four parameters were registered subsequently by their degree as 0, 1 and 2 points with an additional 1 point if fibroid located on the lateral uterine wall (Table 9.3). Depending on total score sum authors suggested their recommendations. In a cases of total score 0–4 it can be performed a low complexity hysteroscopic myomectomy, while for patients with 5–6 total score considered complex hysteroscopic myomectomy with presurgical GnRH analog treatment and/or two-stage surgery. In a case of 7–9 total score they recommend alternative nonhysteroscopic technique. Recently this classification system was revised and recommended by AAGL practice report as practice guidelines for the diagnosis and management of submucous leiomyomas [14].

Pre-surgical Preparation

GnRH Analogues

It has long been known that myomas are estrogen dependent, their size increases during pregnancy and shrink during menopause. GnRH analogues (GnRHa) induce hypogonadism through pituitary desensitization, down regulation of receptors and inhibition of gonadotrophins, this leads to decrease vascularity, resulting in the case of fibroids in a shrinkage of the mass. Because of these features, GnRHa has been found useful in the management of various hormone-dependant tumours, endometriosis and uterine fibroids.

The first successful report of the effect of GnRHa on uterine myomas was by Filicori et al. (1983). Since then many studies were published on this issue. We know that surgery is less technical demanding when myomas are smaller and a complete surgery can be achieve in a single session. The resection of large myomas is associated with increased bleeding during surgery, longer operative time, risk of fluid overload and sometimes with the necessity of repeated operations [10, 15]. GnRHa are commonly used preoperatively before myomectomy so as to reduce the size of a fibroid in order to make surgery easier and safer [16, 17]. On the other hand GnRHa are expensive and have many unpleasant

Table 9.3 Lasmar classification of submucous myomas

Table classification Lasmar et al. (2005)						
Score	Size	Topography	Extension	Penetration	Lateral wall	Total
0	=2 cm	Lower	= 1/3	0		
1	>2a <5 cm	Medium	>1/3 a 2/3	=50 %	+1	
2	>5 cm	Upper	>2/3	= 50 %		
Total score	+	+	+	+	+	=
Table showing the group and the suggested treatment according the highest score obtained						
Score	Group	Recommendations				
0–4	I	Low complexity hysteroscopic myomectomy				
5–6	II	Complex hysteroscopic myomectomy, consider preparing GnRH analog and/or two-stage surgery				
7–9	III	Recommend alternative nonhysteroscopic technique				

side effects such as menopausal symptoms due to estrogen deprivation.

Although the experience in the use of GnRHa for pre surgical preparation of fibroids, the medical evidence to support this practice has been weak. In one side we have observational studies such as Perino et al. [18] and Donnez et al. [19] that reported the use of GnRHa prior to hysteroscopic resection of myomas as useful, while in the other side we have Campo et al. [20] the found that this practice prolonged surgery time.

Recently was published a systematic review of the literature focused on the benefit of the preoperative use of GnRHa in women with submucous myomas, trying to determinate whether this treatment was more effective than placebo/no treatment prior to hysteroscopic resection, in terms of symptomatic relief, ability to complete surgery, operating time, complications and technical difficulties [21]. This publication shows with good quality evidence that there were no differences in terms of symptomatic relief, achieving a complete resection of the fibroid, operative difficulty and surgeon´s satisfaction. Cost analysis was not done in the included studies. There seems to be some benefit in terms of reduction in both operating time and fluid deficit. Kamath et al. conclude that there is inadequate evidence to support the routine use of preoperative GnRHa before hysteroscopic resection of submucous myomas.

Ulipristal Acetate

Since February 2012, ulipristal acetate (UPA) 5 mg/day, is approved in Europe for preoperative fibroid treatment [22].

UPA is a selective Progesterone receptor modulator (SPRM) that potently modulates P-receptor activity [23] with proapoptotic/ antiproliferative effects on fibroid cells [24] and with pharmacokinetic properties supporting once daily dosing [25]. Two short-term (3 months) randomized clinical trials showed that UPA effectively controls HMB and shrinks fibroids [26, 27]. After treatment cessation, menstruation usually returns within 4–5 weeks, but fibroid volume reduction can be sustained for up to 6 months. In addition, treatment with UPA reduced fibroid-associated pain, improved QoL, and revealed no safety concerns [26, 27].

When compared with a GnRHa like leuprolide acetate, both were effective in controlling bleeding with a difference the median times to amenorrhea were 7 days for patients receiving 5 mg of ulipristal acetate and 21 days for those receiving leuprolide acetate. In terms of myoma size reduction there were not significative differences between the treatments, but in the case of the patients treated with leuprolide, the size increased again by 84 % compared with the UPA group in which the sized remained stable during 6 month after treatment was finished [27]. But the big difference is found in the tolerance, moderate-to-severe hot flashes were reported only for 11 % of patients receiving 5 mg of ulipristal acetate and for 40 % of those receiving leuprolide acetate ($P<0.001$).

Recently a new study on long-term safety of the use of UPA 10 mg/day in the treatment of symptomatic myomas was published. It seems that repeated 3-month courses of oral UPA 10 mg once daily effectively control bleeding and pain, reduce fibroid volume, and restore QoL over the long term in many women with symptomatic fibroids, providing an effective and well-tolerated long-term medical treatment for fibroids [28]. It looks like UPA could be an alternative medical treatment for symptomatic myomas avoiding in some cases necessity of surgery.

Clinical trials have also shown that UPA administration can lead to a pattern of benign, nonphysiological, nonproliferative, histological features of the endometrium termed P receptor modulator associated endometrial changes (PAEC). These changes spontaneously reverse over a few weeks to months after cessation of the 3-month UPA treatment. It is important to remember this fact prior to schedule hysteroscopic surgery, sometimes the endometrial thickness is above 16 mm and it will difficult the correct visualization of the endometrial cavity and even will cause the suspension of the procedure. The solution can be either wait until we can check the endometrium's thickness with an ultrasound or to give a gestagene thinning the endometrium prior to the hysteroscopic procedure [29].

Misoprostol for Cervical Ripening

Misoprostol is a stable synthetic prostaglandin E1 analogue used for the prophylaxis and treatment of peptic ulcers resulting from long-term use of nonsteroidal anti-inflammatory drugs. It is inexpensive, can be kept at room temperature, and is associated with few adverse effects. The systemic bioavailability of misoprostol is three times higher after vaginal insertion than after oral administration. Misoprostol has a cervical ripening effect and induces uterine contractions Its ripening effect was shown by numerous clinical studies [30, 31], and is consistent with biological data.

The last systematic review and meta-analysis published by the Cochrane library [32] the conclusion was that misoprostol administration prior to hysteroscopy appears to have a beneficial role in premenopausal patients undergoing hysteroscopy in both the diagnostic and operative setting. In cases in which cervical dilatation is considered as easy, misoprostol may not be routinely administered as it may only increase patients' discomfort without any substantial benefit.

It seems that the use of 400 mg of vaginal misoprostol 12–24 h before hysteroscopy may reduce the pain and the force needed to dilate the cervix, with only mild side effects.

Myomectomy Techniques

There are different factors to think about before we proceed to perform a hysteroscopic myomectomy.

1. We need to know if the lesions are lying entirely or mostly in the uterine cavity or has a major intramural component. In this case, **should the myometrial free margin still be considered a limiting factor**? Some authors think that should be a limit [33] and a one-step hysteroscopic myomectomy may be performed to remove deeply infiltrating submucous myomas when myometrial thickness at the implantation site is as more than 5 mm. But, is this fact a real limitation? In another study [34] was evaluated the feasibility of the hysteroscopic resection of type II submucous fibroids regardless of the myometrial free margin separating them from the serosa. In this work the authors reported the dynamic changes the margin undergoes after the various phases of resection. During the hysteroscopic myomectomy ultrasound evaluation of myometrial free margin was measured before and alter each phase of the procedure. They found that myometrial free margin increases progressively with each step of the procedure probably leading to an increasing margin of safety. The importance of this margin is in the risk of perforation during the myomectomy, but it depends on the myome type and on the surgical technique, when the myoma is a type 2–5 traversing the myometrium and reaching the uterine serosa and the procedure is one step resectoscopy, in such circumstances it be neither feasible nor safe.
2. The **cleavage plane**, it is the space between the fibroid and the adjacent myometrial tissue, also called "**myoma pseudocapsule**". This space contains a proper vascular network, there isn´t any true vascular pedicle. The myoma is anchored to the pseudocapsule by connectival bridges. At this level there different elements such smooth muscle cells similar to the myometrium, neuropeptides and angiogenesis factors, this ultrastructural feature suggests that when removing fibroids their pseudocapsules should be preserved as much as possible, in order to preserve the myometrium [35, 36]. Depending of on the myoma type there are myomectomy techniques that respect this important cleavage plane, such as those that enucleate the myoma.

Today the tendency is to perform surgery in an outpatient setting, and this is also the tendency in hysteroscopy. New techniques and new instruments were developed during the last decade that allows us to perform office hysteroscopic myomectomy. We are going to review all the most used surgical option for submucous myomas, but only few are performed in an office setting.

Resectoscopy

This is the most commonly employed approach. The resectoscope is the instrument that resects

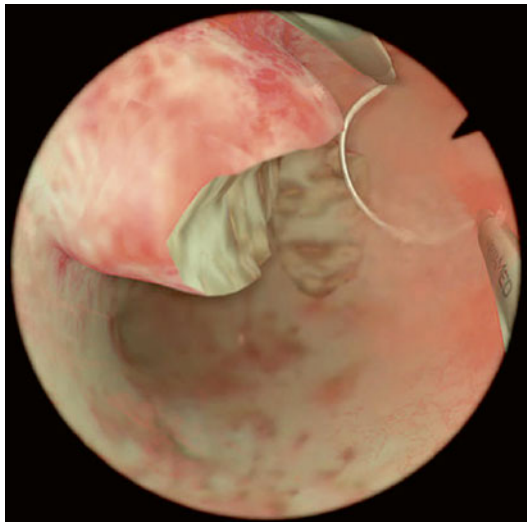

Fig. 9.6 Resectoscopy of a myoma

under direct and constant visual control. The sheath has an outer diameter of 7–9 mm, and includes both inflow and outflow ports for distending media. The resectoscope is equipped with continuous flow and provides excellent irrigation for operative procedures. If surgical debris or the so-called 'chips' block the operative field, the resectoscope can be removed while the sheath is left in place. This allows for removal of large tissue while maintaining cervical dilatation. It has a straight-forward or a slightly fore-oblique telescope 12/30° [37].

Because of the diameter of the endoscope, most of the times it requires cervical dilatation. It is performed with an inpatient in surgery room under anesthesia (see Fig. 9.6).

The distending solution depends on the electrosurgical system, if it is a monopolar system it will require a non conducting distending solution such as sorbitol 5 % or glycine 1.5 %, but if the system is bipolar the use of normal saline solution is allowed, avoiding the risk for the patient of excessive fluid absorption and the potential electrolyte imbalance [38, 39]. Fluid input and output should still also be monitored. If excessive intravasation occurs, the isotonic fluid overload is generally readily treatable with diuretics (e.g. furosemide 20 mg intravenously). Therefore, a higher amount of intravasation during surgery can be accepted. Generally, most protocols and guidelines mention about 2,500 ml as the upper limit of saline intravasation.

This endoscope uses a radiofrequency electrosurgical generator. The electrosurgical system can be monopolar or bipolar: in the monopolar one, from the extremity of the resectoscope (active electrode) the flow of current, in order to close the circuit, must reach the plate (passive electrode). The use of a bipolar set of instruments, in which both electrodes are introduced into the thermal loop, would be much safer. In this way the current will only have to pass through the tissue with which the thermal loop comes into contact, thus minimizing the danger deriving from the random passage through the corporeal structures. The passage of the electrical energy from the thermal loop to the tissues determines the cutting or coagulation action of the resectoscope. There are various types of thermal loops with different shapes and sizes. The diameters of thermal loops for bipolar resectoscopes are usually smaller than loops for a monopolar instrument with the same outer diameter, thus increasing the time required for resection (Indman 2006). The bipolar loop operates in a similar way to a monopolar electrode; however, as tissue contact is not necessary for activation, the electrodes do not 'stick' in the tissue while cutting (Stamatellos and Bontis 2007). Although bipolar techniques are less hazardous because of intravasation and electrolyte blood-imbalances, more gas-bubbles may hamper visualisation, and gas-embolimight even cause spasms in the lung capillaries, potentially disturbing gas diffusion in the lungs.

The removal of type-0 and most type-1 lesions is generally straightforward. It consists of repeated and progressive passages of the cutting loop beyond the myoma, with cutting only taking place during the backward or return movement of the loop. Excision usually begins from the top of the fibroid, progressing in an uniform way towards the base, it is also the technique for pedunculated fibroids. The surgery is considered finished when the fasciculate structure of the myometrium is visualized. In some cases this technique is associated to a lack of clear vision

due to the accumulated fragments of fibroid in the cavity, the classical removal of tissue under visual control with the resectoscope may consume a lot of time, a resectoscope with automatic chip aspiration could be of help, or consider the use of a morcellator.

G1 and G2 fibroids should not exceed 5–6 and 4–5 cm respectively in order to succeed to remove them hysteroscopically. Although in some cases they can be removed by one-step procedure, most surgeons prefer to remove this kind of myomas through a two-steps procedure (Loffer 1990).

Myoma growth within the uterine wall produces dislocation, compression, and stretching without rupture of adjacent muscle fibers. When the intramural portion is resected by classic slicing technique, direct cut with the loop and thermal damage may cause injury to adjacent healthy myocytes.

For deep type 1 and type 2 there is a high risk of damage of the healthy myometrium during electrosurgery, both by cutting and by thermal damage. Other risks are bleeding, intravasation and the risk of perforation. In case of lesions that extend close to the serosa, within a few millimeters, sometimes there may be a role for the concomitant performance of laparoscopy, not necessarily because it reduces the chance of perforation, but because it allows for the creation of a safe buffer of gas around the uterus should perforation occur. Alternatively, intraoperative transabdominal ultrasonography can be performed when performing dissection of leiomyomas that are believed to be close to the uterine serosa [40].

In some cases it is possible to use a cold loop, those are structurally more robust than others as they are used in a mechanical way without electrical energy to carry out enucleation of the intramural component of the myoma.

Morcellator

Currently we can find in the market three different hysteroscopic morcellators, the Truclear (Smith and Nephew, Andover MA, USA), the Myosure by Hologic (Bedford MA, USA) and another company that recently introduced an alternative device is Storz (Tuttlingen, Germany).

The TRUCLEAR system approved by the FDA in 2005, is based on an instrument that consists of a set of two metal hollow rigid tubes that fit into each other [35]. The inner tube rotates within the outer tube, is driven mechanically by an electrically powered control unit, and is controlled by a foot pedal that activates the rotation and regulates the direction of rotation of the inner tube. The control unit is connected to a handheld motor drive unit in which the morcellator is inserted.

Both tubes have a window-opening at the end with cutting edges. By means of a vacuum source connected to the inner tube, the tissue is sucked into the window-opening, cut and 'shaved' as the inner tube is rotated [41]. The system uses no electrocoagulation, and there is no lateral thermal or electrical energy spread. Haemostasis occurs by spontaneous myometrial contraction. The removed tissue is discharged through the device, is collected in a tissue-trap, and is available for pathology analysis. As only one introduction is needed, the number of perforations is extremely low. The 4.0-mm morcellator is introduced in the uterine cavity through a straight-forward working-channel of a continuous flow 8–9 mm rigid hysteroscope. After dilatation of the internal orifice of the uterine cervix, atraumatic insertion is accomplished with the use of an obturator in the outer sheath of the hysteroscope.

Saline solution is used for distension and irrigation.

van Dongen et al. [42], conducted a randomised-controlled trial (RCT) to compare conventional resectoscopy and hysteroscopic morcellation among residents in training. The mean operating time for resectosocpy and morcellation was 17.0 (95 % confidence interval [95 % CI] 14.1–17.9, standard deviation (SD) 8.4) and 10.6 (95 % CI 7.3–14.0, SD 9.5) min, respectively ($P<0.008$). Subjective surgeon and trainer scores for convenience of technique on a visual analogue scale were in favour of the morcellator.

A new development in hysteroscopic morcellation is the recent availability of a smaller outer diameter TRUCLEAR system, with a 2.9-mm cutting-blade and a 5.0-mm hysteroscope for

office or ambulatory use with no or local anaesthesia. Polyps, small myomas, and retained products of pregnancy can be removed in that way.

MyoSure® Tissue Removal System (Hologic, Bedford, MA), was approved by the FDA in 2009; this morcellator consists of an electrical control box, a foot pedal, and a morcellator hand piece that features a rotating/reciprocating 2 mm OD cutter blade encased in a 3 mm OD outer tube. The cutter is connected to a vacuum source that aspirates resected tissue through a side-facing cutting window in the morcellator's outer tube. Resected tissue is captured in a standard vacuum canister tissue trap and is available for pathological examination [43].

Regardless of the methodology used to resect intrauterine pathology, it is important to remember that resected tissue must be thought of in terms of three-dimensional rather than two-dimensional measurements. Thus, increasing pathology diameter yields a exponential rather than linear increase in volume following the equation $\nu = \pi d^3/6$. This mathematical consideration becomes important as one plans a surgical approach for submucous myomas in which the resection rate and procedure time will be a function of the volume, density, and type of myoma tissue. With loop resectoscopy, the amount of tissue removed per minute will depend on:

1. How quickly the surgeon deploys each pass of the loop
2. How much tissue each bite with the loop resects
3. How quickly the tissue chips can be removed from the uterine cavity.

On the other hand, with hysteroscopic morcellation, the amount of tissue removed per minute will only be a function of [1] how much contact the cutting window maintains with the myoma and [2] how quickly the device can cut tissue and aspirate it out. Because the devices' cutting speeds are relatively fixed by their design characteristics, minimizing procedure time mostly depends on maintaining tissue contact between the cutting window and the pathology. Learning the correct resection technique, although not difficult, is of prime importance with hysteroscopic morcellation.

Although in vivo accurate measurements of tissue resection speed are challenging to conclusively determine due to surgeon and pathology variations, in vitro measurements have been performed to assess the tissue resection characteristics of the different devices. As part of an IRB-approved FDA submission study in 2008, the author (JAG) compared a working MyoSure device prototype with a TRUCLEAR device to assess tissue resection speed. Fresh, discarded uterine leiomyoma tissue was placed in a saline-filled container and each device was placed directly on the tissue in alternating 5-min intervals for 30 min. The trial was repeated on three different myoma specimens. The study was designed to compare tissue cutting on identical tissue and to assess decline of cutting speed over time as a result of blade dulling [44]. As these data demonstrate, both devices are capable of resecting submucous myomas 3 cm in diameter (~15 cc^3) in 15 min or less, although the MyoSure device was consistently faster at tissue removal at every time interval despite its smaller diameter.

In addition, the smaller diameter of the MyoSure hysteroscope (6.25 mm) compared with the TRUCLEAR hysteroscope (9.0 mm) makes the MyoSure device potentially more compatible with an oral sedation/cervical block anesthesia protocol and therefore amenable to office-based treatments of polyps and Type 0 or I submucosal fibroids [45].

Although promising, at this moment the level of evidence for the use of hysteroscopic morcellator for submucous fibroids is limited, more trials are needed [43].

Vaporization

The resectoscope can also fit bipolar and monopolar vaporizing electrodes; the power required to vaporize tissue is 150–300 W of pure cut current delivered by any electrosurgical generator ([46]; Vilos and Abu-Rafea 2005). The vaporizing electrodes are also useful mechanical tools to be used to dissect the fibroid from its bed without electrosurgical activation. Ideally such vaporization results in no tissue fragments, with the tumor gradually reduced in volume until it is feasible to extract the residual mass with grasping forceps

[46], or morcellator. The depth of vaporization depends on the duration of contact, resistance and wattage of the generator. In order to avoid uterus perforation, the electrode must move slowly across the tissue, only towards the operator without applying prolonged pressure in one spot. Available but lower quality evidence suggests that this advantage may be seen in hysteroscopic myomectomy [47, 48].

Although argon, krypton and neodymium-yttrium-aluminum garnet (Nd:yAG) lasers have all been successfully used, only the latter has found widespread application in hysteroscopic surgery (Ubaldi 1995), being very popular in the late 1980s and early 1990s. Two techniques 'touch' and 'non-touch' may be used in hysteroscopic Nd:yAG laser surgery for fibroids of 2 cm or less (Goldrath et al. 1981; Loffer 1987). In the former, the laser fiber is in contact with the surface to be treated coagulating first the surface vessels and then the fiber is dragged repetitiously over the fibroid until is flattened, whereas in the latter it is separated from it by a few millimeters. In hysteroscopic myomectomy both techniques were used (Ubaldi 1995). Not in use because of the high cost.

Hysteroscopic Outpatient laser applications (HoLA by Biolitec, Germany), it is a diode laser with a power of 120 W using a Myofiber of 9 Fr for submucous myoma vaporization in an office setting. Although it is effective for fibroid tissue vaporization it has some limitations:

1. The fiber diameter requires a 6.3 mm hysteroscope that is not well tolerated by most of the patient without anesthesia
2. The power of 120 W is necessary in order to achieve tissue vaporization, the heat created by the laser is painful for the patient when it is used near the myometrium.
3. Lack of specimens for histopathology analysis
4. The level of evidence for the use of diode laser for fibroids vaporization is limited and more trials are needed.

Laser

In our unit we started to use Diode Laser for the treatment of endometrial pathology in 2007, in an office setting without speculum, tenaculum or anesthesia. At the beginning we used a 400 μm fiber, to flexible for myoma but enough for polyps. In 2008 after describing the characteristics of the fiber we needed, we got a 1,000 μm, rigid and conical fiber. We this fiber there was no limit for treatment, polyps, septum, synequiae and myomas. We used a 4.3 mm continuous flow office hysteroscope (Bettocchi Office Hysteroscope "size 4" (Karl Storz, Tuttlingen, Germany) with a 2.9 mm rod lens optical system. We didn´t use the external aspiration sheath so diameter got reduced from 5 to 4.3 mm. Distension of the uterine cavity was obtained with saline solution.

First we were limited to myoma G0 and some G1, because we couldn´t access the intramural component of the fibroid. With G0 fibroids we just cut the pedicle independent of myomas size and tissue sample was sent for analysis. If because of dimensions the extraction was impossible we just left the myoma inside the uterine cavity. With some G1 fibroids we just made an incision with the laser on the endometrial mucosa in the base of the fibroid and looked for the cleavage plane where we just cut the connectival bridges to the myometrium until total enucleation (see Figs. 9.7 and 9.8). Again, if the enucleated myoma was to big for the extraction, after taking tissue sample for analysis, it was left inside the uterine cavity.

Our challenge were the G2 and deep G1 fibroids, untill in 2009 Bettocchi et al. [49] described a new hysteroscopic technique for the office preparation of partially intramural myomas to facilitate the subsequent scheduled resectoscopic myomectomy. The procedure consists of an incision of the endometrial mucosa and the pseudsocapsule covering the myoma aimed at facilitating protrusion (see Fig. 9.9) of the intramural portion of the myoma into the uterine cavity as a preliminary step for in-patient resectoscopic surgery after two menstrual cycles. At follow-up hysteroscopy, the conversion of myomas with partially intramural development into totally or prevalently intracavitary ones was observed in 55 out of 59 patients (93.2 %).

Based on Bettocchi results we developed a new two-step technique for G2 and deep G1

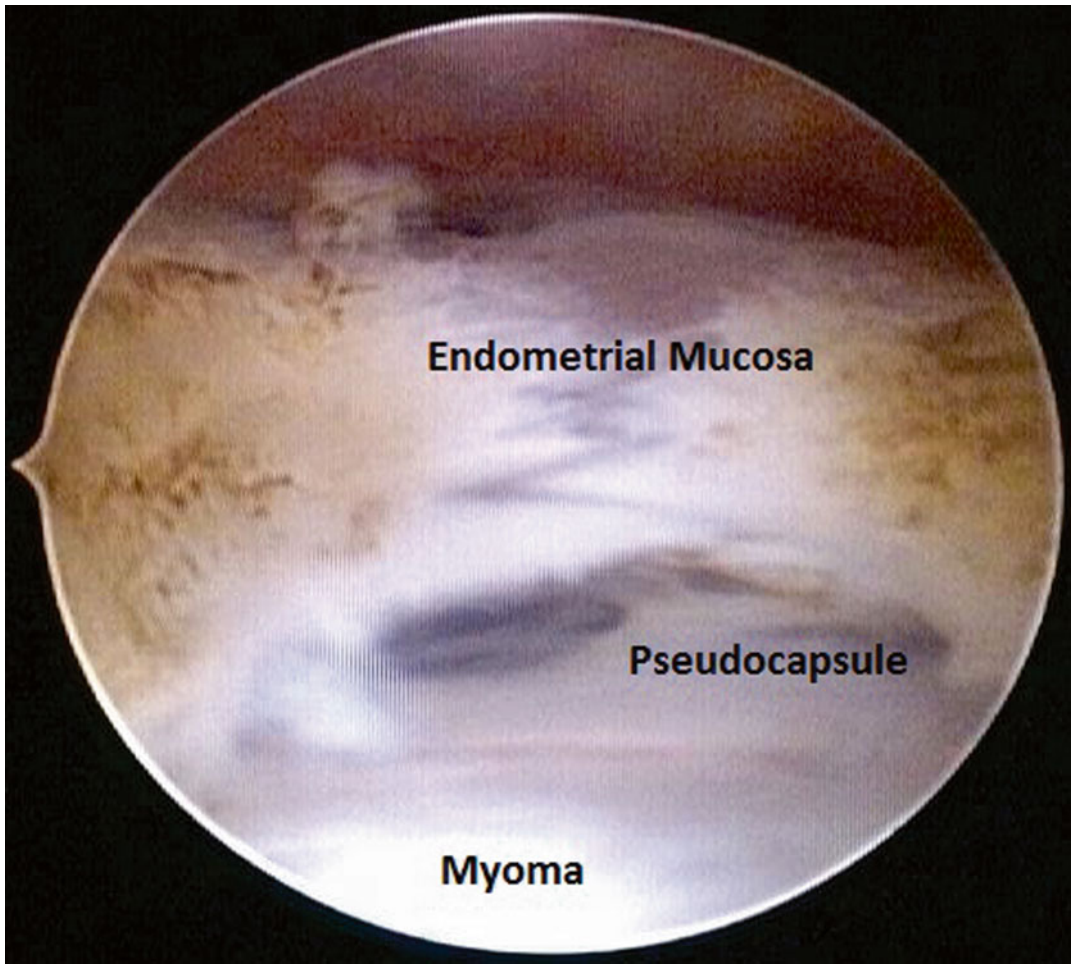

Fig. 9.7 Cleavage plane of pseudocapsule

fibroids, in which both steps were in office setting without anesthesia [50]. The first step was the same as Bettocchi´s technique, and second step for excision of the myoma was performed four weeks later using the same hysteroscope and setup (pressure, flow, suction) as those used for the first office procedure. The myoma was excised by means of diode laser or with mechanical instrumentation technique (scissors and grasping forceps). In those patients in which extraction of the myoma was not possible due to the size of the mass, the myoma was left free in the uterine cavity, and an ultrasound check-up was performed 2 months later to assess the presence or absence of myoma remnants.

The median (IQR) operating time was 16 [10, 12–19] min for the first step and 24 [21–28] min for the second step. All patients were discharged within 30 min after finishing the procedure and no major complications were reported during or immediately after the hysteroscopic procedures. As shown in Table 9.4, success of surgery was significantly associated with size, location, and women's parity. All myomas <18 mm were successfully enucleated as compared with 85 % of 19–30 mm, and 0 % of >30 mm ($P < 0.001$).

At the second step office hysteroscopy, the conversion of myoma with partially intramural development into totally (G0) or mainly

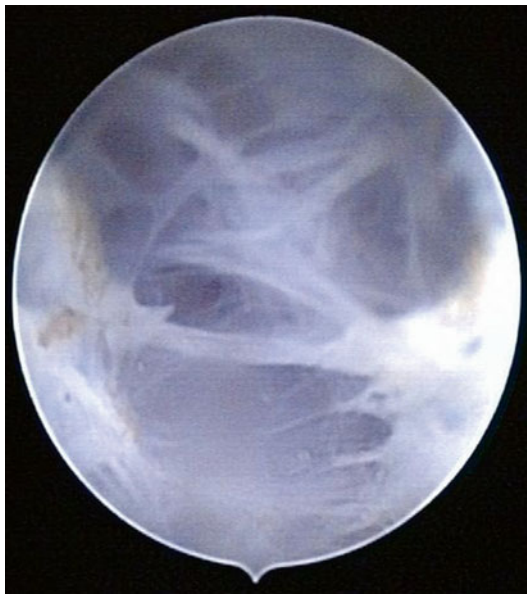

Fig. 9.8 Connective bridges in the pseudocapsule

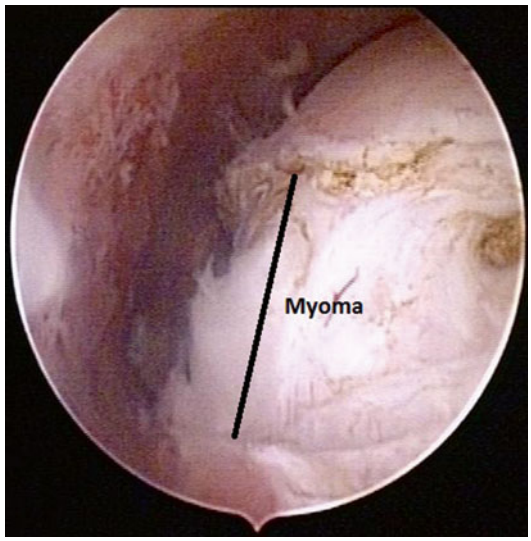

Fig. 9.9 Myoma's protrusion after cutting the pseudocapsule

intracavitary (<50 %) (G1) ones was observed in 95.3 % (41/43) of cases.

With this technique, preserving the integrity of adjacent fibers, avoids disruption of the uterine wall and ensures a successful outcome, especially in young women who desire future childbearing. Moreover, this technique represents the natural transposition of surgical principles of laparotomic myomectomy to operative hysteroscopy. The incision of endometrium that covers the myoma, and obtainment of a perfect cleavage space between myoma and adjacent healthy fibers allow protrusion of the intramural portion. The myoma is transformed from G2 or G1 to G0 and enucleation is facilitated. The result is complete enucleation without injury to the uterine wall and reduced risks associated with classic slicing.

We realized that with myoma >30 mm we had technical limitation because a lack of surgery field during the second step, based on the relation of the protrusion of the fibroid and the cavity size. Last year we introduced the vaporizing laser in order to reduce mass and we improved our results with enucleation of fibroids up to 5 cm.

Updated to April 2014 we already reached 117 myomas G2 and G1 operated with this technique with better results.

Our technique respects the pseudocapsule and is less traumatic for the tissues. Regarding the enucleated fibroid that we leave in the cavity, we have follow up 61 cases, and in the ultrasound performed 2 months after procedure, the mass disappear in all cases (100 %), as shown in Table 9.5. There were three patients that explained expulsion with pain (4.9 %) and just one of these patients attended the Emergency Department because of pain and was treated with analgesics.

Enucleation in Toto

A technique described by Litta et al. in 2003, for the treatment of myomas with high intramural involvement (G1-G2), that favoring the intracavitary protrusion of the myoma ensures safe removal while minimizing damage to the surrounding myometrium [51]. First under spinal anesthesia, with a 12-degree fore-oblique lens resectoscope and 90- degree Collins electrode, an elliptical incision of endometrial mucosa that covers the myoma was made at the level of its reflection on the uterine wall until the cleavage zone is reached. Connecting bridges between myoma and surrounding myocytes were slowly resected. The effect of this is that the myoma protrudes into the cavity. This fact facilitates its

Table 9.4 Results of the second step on 43 patients

Study variable	Second step office hysteroscopy		*P* value
	Enucleation	Resectoscopy	
Size, mean diameter (mm)			
≤18	17/17 (100)	0	<0.001
19–30	17/20 (85)	3/20 (15)	
>30	0	6/6 (100)	
Location			
Anterior-posterior walls	29/33 (87.9)	4/33 (12.1)	0.020
Fundus-lateral walls	5/10 (50)	5/10 (50)	
Parity			
Nulliparous	21/22 (95.5)	1/22 (4.5)	0.009
Parous	13/21 (61/9)	8/21 (38.1)	

Table 9.5 Outcomes of leaving enucleated myoma in the uterine cavity

Variable	Data	Measure
Size	**N**	**%**
<20 mm	32	52.5
20–29 mm	19	31.1
>30 mm	10	16.4
Hysteroscopic grading	N	%
G0	20	32.8
G1	31	50.8
G2	10	16.4
Localization	N	%
Anterior	24	39.3
Posterior	13	21.4
Lateral	24	39.3
Follow up (days)	Mean	SD
	68.17	16.5
	N	%
Pain	3	4.9
Bleeding	13	21.3
Others	2	3.3
None	43	70.5
Ultrasound scan (follow up) for myoma	N	%
	61	0
Degree of Satisfaction	Mean	Percentile
	4.55	[4–5]

removal by slicing. The myoma is pushed into the uterine cavity, enabling the surgeon to work safely and resect the intramural component completely without affecting the healthy myometrium. Sometimes in myomas over 30 mm a second step procedure was required, and was not considered a failure of the technique. The second step was planned after approximately 50 days after (2 menstruations).

Recently results of a long-term follow up of this technique in 112 women affected by menorrhagia were published [52]. The mean follow-up was over 58 months with a success rate of the procedure of 88.4 %. Only 15 % required a second step procedure. This is a safe technique that enables transformation of the myoma from G2 to G0, allowing the surgeon to perform a completely safe myomectomy within the uterine cavity. This results in reduction of perforation of the uterine wall, which in the published series was null.

'Cold Loop' Myomectomy

This technique, developed by Mazzon [53], is characterized by a sequence of three different operating steps:

1. Excision of the intracavitary component of the fibroid: this is carried out with the usual technique of resectoscope slicing. This action must stop at the level of the plane of the endometrial surface, so that the identification of the passage between the fibroid and the adjacent myometrial tissue is not impaired (cleavage plane).
2. Enucleation of the intramural component of the fibroid: once the cleavage plane is identified the usual cutting loop of the resectoscope is substituted by a suitable blunt dissection cold loop (mechanical loops of Mazzon; Karl Storz, Tuttlingen, Germany). Usually the rectangular loop is used first. This loop, once inserted into the plane between the fibroid and myometrium, is used in a mechanical way

along the surface of the fibroid (usually clearly recognizable by its smooth, white and compact surface), thus bringing about its progressive blunt dissection from the myometrial wall. Then the single tooth loop is used to hook and lacerate the slender connective bridges which join the fibroid and the adjacent myometrium. During the entire phase of enucleation, electric energy must not be used in the thickness of the wall, and the loop must be used 'cold' or in a mechanical way.

3. Excision of the intramural component: at the end of the enucleation phase, the intramural part of the fibroid is totally dislocated inside the uterine cavity. At this point it can be completely and safety excised by means of the usual progressive excision using an angled cutting loop.

In a prospective study published by Mazzon et al. with an important series of 688 women with 806 G1-G2 myomas, the integrity of the uterine cavity and prevalence of intrauterine synechiae were analyzed [54]. In all cases cold loop resectoscopic myomectomy and 2 month after surgery a diagnostic hysteroscopy for follow up. Neither intrauterine device nor anti-adherence mixtures were used at the end of surgery.

The rate of adhesions 2 months after resectoscopic myomectomy was approximately 4 %, of which only 0.29 % was represented by fibrous synechiae. Mazzon et al. believe that the safety of the surgery and the low rate of adherences reported can be ascribed to the nonuse of electricity in coagulation mode (which is characterized by higher thermic damage) and conversely to the use of the cold loop; this procedure prevents electrical energy (of either type, monopolar or bipolar) from coming in contact with the myometrium of the uterine wall and inducing thermic damage (which may increase the appearance of synechiae).

The fibroid was completely removed in one-step procedure in nearly 80 % of cases.

Versapoint (Bipolar Energy) and Mechanical Instruments (Scissors and Forceps)

These instruments are used in office setting hysteroscopy. In some cases of small myomas it is possible to achieve enucleation. According to Bettocchi et al. [55], it is feasible to operate this way, myoma up to 20 mm using a 5 Fr bipolar electrode (Versapoint).

Complications of Hysteroscopic Myomectomy

Traumatic Injuries

Perforation of the uterus can occur with dilators, mechanical grasping tools, or the hysteroscopic/resectoscopic system. If perforation occurs with mechanical instruments, and no bowel injury is suspected, the patient can be observed expectantly. Laparoscopy should be reserved for those circumstances where bowel injury is suspected, where there appears to be a large defect, or in the presence of heavy bleeding. If perforation occurs with an activated electrode, one has to assume that there has been a bowel injury until proven otherwise, and laparoscopy or laparotomy is recommended [56, 57]. Most cases reported of perforation or false route were associated to dilatation prior to resectoscopy/morcellator. The risk of cervical laceration and uterine perforation is reduced with the preoperative use of misoprostol. In a case control study of complications associated with bipolar and monopolar hysteroscopic operations (1,318 in the study group and 524 in the control group), found that the complication rate was 4.1 % in the study group and 2.8 % in the control group ($p=0.08$) [58]. In this study the dilatation/false route rate was of 0.7 and 0.8 %. In a long-term analysis of 1,028 office hysteroscopies no perforation or false routes were found [59].

Excessive Fluid Absorption

Associated to the use of monopolar energy during resectoscopy where a non-crystalloid distension media such as 1.5 % glycine, 3 % sorbitol and 5 % mannitol solutions. is needed. Excess absorption of those can cause serious fluid and electrolyte imbalance, pulmonary and cerebral edema, cardiac failure, and death [38, 39, 60, 61]. If mechanical or bipolar instruments are being utilized then it is possible to use electrolyte-containing solutions, such as normal saline, to

distend the uterus. Such distension media are associated with fewer unfavorable changes in serum sodium and osmolality than the electrolyte free media used with monopolar instruments. Their use, however, does not eliminate the need to prevent excess absorption or to closely monitor fluid balance, as overload can cause pulmonary edema. Bahar et al. found in his case–control study that the media related complication with the use of monopolar resectoscope was of 0.8 % and due to the bipolar resectoscope was of 0.4 % [56]. von Keerkvoorde et al. didn't find any case of excessive absorption of saline solution in his analysis over 1,028 office hysteroscopies [59].

Bleeding

Heavy bleeding from the endometrial cavity is uncommon after hysteroscopic surgery in general. If occurs can be treated with intracervical injection of a prostaglandin F2α analog or intrauterine placement of a balloon/Foley catheter.

Thermal Burns

Thermal injury caused by the use of radiofrequency electricity may be related to the active electrode, the dispersive electrode, or may be caused by current diversion, the latter a circumstance unique to monopolar resectoscopes. More sinister burns occur when the uterus is perforated by an active electrode causing injury to surrounding structures, most commonly the bowel or vessels. At least two deaths are known from injuries to major pelvic vessels during resectoscopic surgery and unrecognized uterine perforation. Avoiding activation of an electrode when it is being advanced largely prevents this type of injury. Another circumstance that could contribute to dispersive electrode injury is the use of bulk vaporization electrodes that require relatively high power settings to generate sufficient current density to create the desired electrosurgical effect. Even with an appropriately attached electrode, thermal injury has been described.

It has been known for some time that electrical burns can occur in association with the use of the monopolar resectoscope. Such injuries result from stray radiofrequency current reaching and being focused on unintended tissue including the vulva, vagina and cervix [62, 63]. The basic mechanism seems to involve current that is directly or capacitively coupled to the resectoscope's external sheath where it normally flows to the surrounding cervix. If the external sheath retains enough contact with the cervix, the current may be dispersed (defocused) and no injury results.

However, if the sheath is not in good contact with the cervix or in the presence of a short and/or scarred cervical canal, the current may flow-from the sheath to whatever tissue it is in contact with, such as the vagina or vulva, potentially causing a burn if a high enough current density is attained [64]. As a result, the surgeon should ensure that the cervix isn't excessively dilated relative to the diameter of the resectoscope and that the external sheath is maintained in the cervical canal whenever the electrode is activated.

Adhesions

Formation of Intra Uterine Adhesions (IUA) after a resectoscopic surgery is a frequently encountered complication.

Gaitras et al. found that 2.4 % of patients undergoing hysteroscopic myomectomy developed postoperative IUA formation [65]. However, some reports demonstrated a frequent occurrence of IUA in the follow-up after hysteroscopic myomectomy, which could be as high as 31.3–45.5 %, depending if it was a solitary myoma or multiple [66]. Yang et al. studied a group of 132 women with a single submucous myoma with a diagnostic hysteroscopy 2 weeks after resection of the fibroid, and found that only 2 (1.5 %) women developed IUA [67]. The results were different if instead of one myoma there were two or more in opposition to each other, the arte of IUA was in this case of 78 %. The low prevalence of postoperative IUA after the resection of a solitary submucous myoma in this report is very likely because the submucous myomas was resected with the one-step method. With this method, the fibroid was completely enucleated without damaging to the adjacent myometrium. The overlying endometrium could therefore be repaired without the formation of IUA at the site of resection. This also one of the reasons why a myomectomy technique has to respect the cleavage

plane preserving the myometrium adjacent, like with the cold loop [54], or the two step enucleation with laser [50]. The method they recommend in order to prevent IUA is the use of an Intra Uterine Device (IUD), over the Foley Balloon due to an increase of infection risk with this method. According to the AAGL Guidelines, a Second-look hysteroscopy may be effective for postoperative intrauterine adhesions and thereby could reduce the long-term risk of adhesion formation [5].

Office Setting

There some minor complications associated to this kind of procedure. Most of them directly related to the pain, like nausea and vomiting as part of a vasovagal reaction. The only way to avoid the vagal attack is to listen to the patient and to stop the procedure when the patient refers pain. In over 2000 laser surgical procedures without anesthesia we had only seven mild vasovagal reactions with spontaneous resolution.

Office Setting – Outpatient vs Inpatient

There aren´t many techniques that allow performing a myomectomy in an office setting, but the tendency due to different reasons, is to perform the procedures in the outpatient.

1. No need for anesthesia: Cicinelli in after a review of the literature concluded that most of the evidence in the literature suggests that office hysteroscopy in experienced hands is a well-tolerated technique and requires the use of analgesics only in selected patients like women with previous caesarean section, history of chronic pelvic pain, anxiety and in menopause [68]. The pain is related to the diameter of the hysteroscope, the use of saline instead of CO_2 for distension [69, 70], the use of vaginoscopic approach without speculum, parity and surgeon skills. Cooper et al. [71]. examined the effect of a vaginoscopic approach to outpatient hysteroscopy on the patients' experience of pain, compared with a traditional approach using a vaginal speculum and tenaculum in a metaanalysis of six RCTs (n = 1,321). They found that vaginoscopic approach to hysteroscopy was less painful than using the traditional technique (standardised mean difference (SMD) _0.44, 95 % CI from −0.65 to −0.22). No significant difference was found in the number of failed procedures between groups.
2. Costs: In a British study was concluded that outpatient see-and-treat hysteroscopy was associated with the lowest treatment costs when comparing with an inpatient [72]. In another study with Spanish population [73] the average cost of outpatient and day-case procedures were analyzed, based on the 1,695 hysteroscopies performed between 2010 and 2012. A model with 10 progressive scenarios was built according to the number of outpatient procedures performed. The economic saving and the number of operating room sessions avoided were analyzed. They showed that performing all the surgical hysteroscopic procedures in an outpatient setting represented a saving of 177.971€ and freed 85.16 surgery rooms days of 7 h each. They recommended that office outpatient hysteroscopic surgical procedures should replace the inpatient theater procedures.

It is clear that a hysteroscopic procedure in an office outpatient setting is cheaper than in an inpatient, but what about a myomectomy? Do we have any evidence to support that it is cheaper? The truth is that at the moment the evidence found is limited, there is only one American study published in 2001 [74] where Surjha et al. compared the cost of different myomectomy techniques (abdominal, laparoscopy and hysteroscopy) and saw that the cost of a hysteroscopic myomectomy was 7,704 USD and 4,291 USD when performed in the inpatient and outpatient setting, respectively.

The myomectomy techniques that can be performed in an office setting without anesthesia are the 2-step procedure with laser and in some cases morcellation (the new Trucelar system for 5 mm hysteroscope). Recently a bipolar resectoscope of 21 Fr for a 7 mm hysteroscope was commercialized but it still to thick for a procedure without anesthesia (Princess™ by Wolf). Some small

myomas can be resected with the versapoint bipolar system or mechanical tools (forceps and scissors).

What Is the Best Technique?

It is hard to answer to this question. The results in the use of the different procedures depend on many factors, as number and type of the submucous fibroid, the size, etc.….

Instead of answering to the question it may be better to describe what are the characteristics that we as clinicians should seek in any myomectomy technique.

1. Successful myoma enucleation
2. Short surgery time
3. Safety
   (a) No traumatic injuries
   (b) Avoid excessive fluid absorption
   (c) No bleeding
   (d) Avoid Thermal Burns
   (e) No post surgery adhesions
4. Preferred in an office setting
5. Preserve fertility
6. Preserve the integrity of subjacent myometrium
7. Cheap (no cost comparative studies)

Based on these characteristics the different techniques will be analyzed depending on the myoma type, G0 or G1-G2.

Myoma G0 (Sessile or Pedunculated)

With this myoma type all the techniques achieve complete surgery. Except the laser procedure that only cuts the pedicle and leaves de myoma in the cavity, with independency to myoma's size. The rest of the techniques extract from the cavity all the fibroid mass and surgery time will depend on the volume (see Fig. 9.10). The traditional resectoscopy (bipolar or monopolar) is the slowest; surgery time is shorter with morcellator and vaporization. In case of small fibroids (up to 20 mm) it is possible to achieve excision with office hysteroscopy techniques. There is no indication for "cold loop" or enucleation in Toto.

In terms of safety, there is risk of excessive fluid absorption with the use of monopolar resectoscopy in long surgery, or even thermal burns. In all the techniques that require cervical dilatation there is a probability of perforation or false routes. In G0 type surgery the risk of adhesions

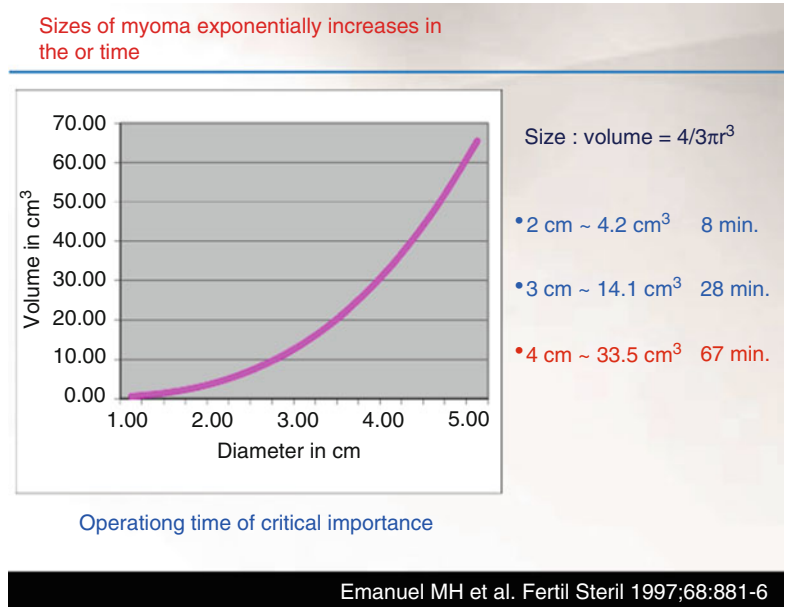

Fig. 9.10 Relation between surgery time and myoma size (page 22)

or bleeding is very low. The subjacent myometrium is preserved with all the different procedures as well as the fertility.

All the office-setting procedures have a lower cost compare to those that are performed in surgery room, even as outpatient.

Myoma G1 or G2

Is in these myoma types where the differences among the procedures are best appreciated. Some of the risk remains equal for the different techniques, such as perforation or false route whenever dilatation is required.

Again, the size together with the proportion of the intramural portion will be the determinant factors of the risk in each technique.

Resectoscopy with Monopolar Energy

This technique will achieve successful surgery in a one step procedure in most G1 type myoma and in some of the G2 type. In cases of deep fibroids there is an increased risk of uterine wall injury, depending on the distance to the serosa, and a second procedure will be necessary in order to extract the intramural portion. The risk of excessive fluid absorption (that will limit the operation time) and thermal burns also exists together with bleeding. The resectoscopy technique is also responsible of the adjacent myometrium injury, with increased risk of adhesions and associated fertility problems. Always in surgery room and anesthesia is needed.

Resectoscopy with Bipolar Energy

The risks are the same as with monopolar with one exception, the possibility of using a saline solution as distension media decreases the risk of excessive fluid absorption. For that reason it is slowly changing the monopolar system in the hysteroscopy units and probably will become the gold standard because there is no need to learn a new procedure, the bipolar just improves the existing.

"Cold Loop" and Enucleation at Toto

These techniques can be performed with a monopolar o bipolar resectoscope with the risk associated described before. The advantage of these two procedures is that they preserve the integrity of the subjacent myometrium with a low risk of adherences, posterior fertility is preserved. Because they are based on converting a G2 o G1 myoma into a G0 there is almost no risk of uterine wall injury and most procedures can achieve the fibroid enucleation in just one-step operation increasing the percentage of surgery success. Learning the technique is required.

Vaporization

Resectoscope with monopolar vaporizing electrodes, with this device the myoma volume is reduced, to facilitate the posterior extraction with the resectoscope. Same conditions as described before with the monopolar resectoscopy. By vaporizing the fibroid volume the probability of surgery success in a one step procedure is increased and surgery time is reduced. Due to the high potency of the laser (120–300 W) surgeon must be very careful due to the risk of uterine wall perforation and the possibility of bowel injury. The Nd:yAG laser is not in use.

The Diode Laser is similar to the monopolar vaporizing electrodes with the advantage that can be used with saline solution; it is a quick way to reduce the myoma's volume. In some cases it can be performed in an office setting thanks to the 6.3 mm diameter. All the vaporization techniques do not preserve the integrity of the myometrium subjacent. Requires experience with the procedure.

Morcellator

The major advantages are the ease of removal of tissue fragments through the instrument and the use of saline solution instead of electrolyte-free solutions used in monopolar high frequency resectoscopy.

It seems that the technique is easier to learn than resectoscopy. van Dongen et al. [42] conducted a randomised-controlled trial (RCT) to compare conventional resectoscopy and hysteroscopic morcellation among residents in training. The mean operating time for resectosocpy and morcellation was 17.0 (95 % confidence interval [95 % CI] 14.1–17.9, standard deviation (SD) 8.4) and 10.6 (95 % CI 7.3–14.0, SD 9.5) minutes, respectively (P = 0.008). Subjective surgeon and

trainer scores for convenience of technique on a visual analogue scale were in favor of the morcellator. Regarding the integrity of the myometrium, it is not clear that this procedure preserves it. More experience is needed in order to determinate the effect on post surgery adherences and in the fertility after procedure.

Laser

The 2-step procedure with diode laser is performed as an office setting procedure, with a 4.3 mm hysteroscope. Achieve enucleation in 92 % of the myomas up to 30 mm [49]. No need for dilatation with a low risk of perforation, saline solution as distension media without risk of excessive fluid absorption. This technique uses the cleavage plane for the myoma enucleation, preserves the integrity of subjacent myometrium. No adherences post surgery, preserves fertility. Requires experience with the technique and it is limited to those patients that tolerate the procedure without anesthesia.

From the data exposed it is understandable that the perfect hysteroscopic myomectomy technique does not exists. Each procedure has advantages and disadvantages, and is up to the surgeon and his experiences to choose what is for him and his patients the best technique, and the choice must be based on lowering risk and improving long-term results. If we follow these principles we will be in a position to say that we are using the best hysteroscopy myomectomy technique.

References

1. Valle RF, Sciarra JJ. Hysteroscopy, contact hysteroscopy, and microhysteroscopy: chapter 118. In: Sciarra JJ, et al., editors. Gynecology and obstetrics 2004 on CD-ROM orders. Hagerstown: Lippincott Williams & Wilkins. http://www.glowm.com/resources/glowm/cd/pages/v1/v1c118.html.
2. Lindheim SR, Kavic S, Shulman SV, Sauer MV. Operative hysteroscopy in the office setting. J Am Assoc Gynecol Laparosc. 2000;7:65–9.
3. Bettocchi S, Ceci O, Nappi L, et al. Operative hysteroscopy without anesthesia: analysis of 4863 cases performed with mechanical instruments. J Am Assoc Gynecol. 2004;11:59–61.
4. Ubaldi F, Tournaye H, Camus M, Van der Pas H, Gepts E, Devroey P. Fertility after hysteroscopic myomectomy. Hum Reprod Update. 1995;1(1):81–90.
5. AAGL Advancing Minimally Invasive Gynecology Worldwide. AAGL practice Report: Practice Guidelines for the diagnosis and management of submucous leiomyomas. J Minim Invasive Gynecol. 2012;19:152–71.
6. Hallez JP. Single-stage total hysteroscopic myomectomies: indications, techniques, and results. Fertil Steril. 1995;63:703–8.
7. Munoz JL, Jimenez JS, Hernandez C, Vaquero G, Perez Sagaseta C, Noguero R, Miranda P, Hernandez JM, De la Fuente P. Hysteroscopic myomectomy: our experience and review. JSLS. 2003;7:39–48.
8. West CP, Lumsden MA. Fibroids and menorrhagia. Baillieres Clin Obstet Gynaecol. 1989;3(2):357–74.
9. Pritts E, Parker W, Olive D. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril. 2009;91:1215–23.
10. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstet Gynecol. 1993;82(5):736–40.
11. Wamsteker K, de Block S. Diagnostic hysteroscopy: technique and documentation. In: Sutton CJG, Diamond M, editors. Endoscopic surgery for gynecologists. London: WB Saunders; 1993. p. 263–76.
12. Munro MG, Critchley HO, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011;113(1):3–13.
13. Lasmar RB, Barrozo PR, Dias R, Oliveira MA. Submucous myomas: a new presurgical classification to evaluate the viability of hysteroscopic surgical treatment – preliminary report. J Minim Invasive Gynecol. 2005;12(4):308–11.
14. American Association of Gynecologic Laparoscopists (AAGL): Advancing Minimally Invasive Gynecology Worldwide. AAGL practice report: practice guidelines for the diagnosis and management of submucous leiomyomas. J Minim Invasive Gynecol. 2012;19(2):152–71.
15. Mavrelos D, Ben Nagi J, Davies A, Lee C, Salim R, Jurkovic D. The value of pre operative treatment with GnRH analogues in women with submucous fibroids: a double blind, placebo-controlled randomized trial. Hum Reprod. 2010;25:2264–9.
16. Somigliana E, Vercellini P, Daguati R, Pasin R, De Giorgi O, Crosignani PG. Fibroids and female reproduction: a critical analysis of the evidence. Hum Reprod Update. 2007;13:465–76.
17. Romer T, Schmidt T, Foth D. Pre- and post-operative hormonal treatment in patients with hysteroscopic surgery. Contrib Gynecol Obstet. 2000;20:1–12.
18. Perino A, Chianchiano N, Petronio M, Cittadini E. Role of leuprolide acetate depot in hysteroscopy surgery: a controlled study. Fertil Steril. 1993;59:507–10.
19. Donnez J, Schrurs B, Gillerot S, Sandow J, Clerck F. Treatment of uterine fibroids with implants of gonadotrophin releasing hormone agonista:

assessment by hysterography. Fertil Steril. 1989; 51:947–50.
20. Campo S, Campo V, Gambadauro P. Short term and long term results of resectoscopic myomectomy with and without pretreatment with GnRH analogs in premenopausal women. Acta Obstet Gynecol Scand. 2005;84:756–60.
21. Kamath M, Kalampokas E, Kalampokas T. Use of GnRH analogues pre-operatively for hysteroscopic resection of submucous fibroids: a systematic review and meta-analysis. Eur J Obstet Gynecol. 2014;177:11–8. doi:10.1016/j.ejogrb.2014.03.009.
22. Melis GB, Piras B, Marotto MF, Orru MM, Maricosu G, Pilloni M, et al. Pharmacokinetic evaluation of ulipristal acetate for uterine leiomyoma treatment. Expert Opin Drug Metab Toxicol. 2012;8:901–8.
23. Gainer EE, Ulmann A. Pharmacologic properties of CDB(VA)-2914. Steroids. 2003;68:1005–11.
24. Horak P, Mara M, Dundr P, Kubinova K, Kuzel D, Hudecek R, et al. Effect of a selective progesterone receptor modulator on induction of apoptosis in uterine fibroids in vivo. Int J Endocrinol. 2012;2012:436174.
25. Pohl O, Osterloh I, Gotteland JP. Ulipristal acetate—safety and pharmacokinetics following multiple doses of 10–50 mg per day. J Clin Pharm Ther. 2013;38:314–20.
26. Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. N Engl J Med. 2012;366:409–20.
27. Donnez J, Tomaszewski J, Vazquez F, Bouchard P, Lemieszczuk B, Baro F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med. 2012;366:421–32.
28. Donnez J, Vazquez F, Tomaszewski J, Nouri K, Bouchard P, Fauser B, Barlow D, Palacios S, Donnez O, Bestel E, Osterloh I, Loumaye E, for the PEARL III and PEARL III Extension Study Group. Long-term treatment of uterine fibroids with ulipristal acetate. Fertil Steril. 2014;101(6):1565–73.e1–18. doi:10.1016/j.fertnstert.2014.02.008.
29. Kodama M, Onoue M, Otsuka H, Yada-Hashimoto N, Saeki N, Kodama T, Wakasa T, Funato T. Efficacy of dienogest in thinning the endometrium before hysteroscopic surgery. J Minim Invasive Gynecol. 2013;20:790–5.
30. Barcaite E, Bartusevicius A, Railaite R. Nadisauskiene vaginal misoprostol for cervical priming before hysteroscopy in perimenopausal and postmenopausal women. Int J Gynaecol Obstet. 2005;91:141–5.
31. Waddell G, Desindes S, Takser L, Beauchemin MC, Bessette P. Cervical ripening using vaginal misoprostol before hysteroscopy: a double-blind randomized trial. J Minim Invasive Gynecol. 2008;15:739–44.
32. Polyzos NP, Zavos A, Valachis A, Dragamestianos C, Blockeel C, Stoop D, Papanikolaou EG, Tournaye H, Devroey P, Messinis IE. Misoprostol prior to hysteroscopy in premenopausal and postmenopausal women. A systematic review and meta-analysis. Hum Reprod Update. 2012;18(4):393–404.
33. Yang JH, Lin BL. Changes in myometrial thickness during hysteroscopic resection of deeply invasive submucous myomas. J Am Assoc Gynecol Laparosc. 2001;8(4):501–5.
34. Casadio P, Youssef AM, Spagnolo E, Rizzo MA, Talamo MR, De Angelis D, Marra E, Ghi T, Savelli L, Farina A, Pelusi G, Mazzon I. Should the myometrial free margin still be considered a limiting factor for hysteroscopic resection of submucous fibroids? A possible answer to an old question. Fertil Steril. 2011;95:1764–8.
35. Malvasi A, Cavallotti C, Morroni M, Lorenzi T, Dell'Edera D, Nicolardi G, Tinelli A. Uterine fibroid pseudocapsule studied by transmission electron microscopy. Eur J Obstet Gynecol Reprod Biol. 2012;162:187–91.
36. Malvasi A, Tinelli A, Rahimi S, D'Agnese G, Rotoni C, Dell'Edera D, Tsin DA, Cavallotti C. A three-dimensional morphological reconstruction of uterine leiomyoma pseudocapsule vasculature by the Allen-Cahn mathematical model. Biomed Pharmacother. 2011;65:359–63.
37. Di Spiezio A, Mazzon I, Bramante S, Bettocchi S, Bifulco G, Guida M, Nappi C. Hysteroscopic myomectomy: a comprehensive review of surgical techniques. Hum Reprod Update. 2008;14(2):101–19.
38. Baggish MS, Brill AI, Rosensweig B, Barbot JE, Indman PD. Fatal acute glycine and sorbitol toxicity during operative hysteroscopy. J Gynecol Surg. 1993;9:137–43.
39. Istre O, Bjoennes J, Naess R, Hornbaek K, Forman A. Postoperative cerebral oedema after transcervical endometrial resection and uterine irrigation with 1.5 % glycine. Lancet. 1994;344:1187–9.
40. Coccia ME, Becattini C, Bracco GL, Bargelli G, Scarselli G. Intraoperative ultrasound guidance for operative hysteroscopy. A prospective study. Reprod Med. 2000;45:413–8.
41. Emanuel MH, Wamsteker K. The intrauterine morcellator: a new hysteroscopic operating technique to remove intrauterinepolyps and myomas. J Minim Invasive Gynecol. 2005;12:62–6.
42. van Dongen H, Emanuel MH, Wolterbeek R, et al. Hysteroscopic morcellator for removal of intrauterine polyps and myomas: a randomized controlled pilot study among residents in training. J Minim Invasive Gynecol. 2008;15:466–71.
43. Miller C, Glazerman L, Roy K, Lukes A. Clinical evaluation of a new hysteroscopic morcellator—retrospective case review. J Med. 2009;2(3):163–6.
44. Greenberg JA, Adam R, Chin A, Sullivan R. Ex-vivo myoma morcellation. Data on file with Interlace Medical, Inc.; 2008.
45. Lukes AS. MyoSure® tissue removal system—comparative sedation study in an office setting. J Minim Invasive Gynecol. 2007;17(6 Suppl):S67.
46. Brooks PG. Resectoscopic myoma vaporizer. J Reprod Med. 1995;40:791–5.
47. Vercellini P, Oldani S, DeGiorgi O, Cortesi II, Moschetta M, Crosignani PG. Endometrial ablation

with a vaporizing electrode in women with regular uterine cavity or submucous leiomyomas. J Am Assoc Gynecol Laparosc. 1996;3:S52.
48. Mark H. Glasser endometrial ablation and hysteroscopic myomectomy by electrosurgical vaporization. J Am Ass Gynecol Laparosc. 1997;4(3):369–74.
49. Bettocchi S, Di Spiezio SA, Ceci O, et al. A new hysteroscopic technique for the preparation of partially intramural myomas in office setting (OPPIuM technique): a pilot study. J Minim Invasive Gynecol. 2009;16:748–54.
50. Haimovich S, Mancebo G, Alameda F, Agramunt S, Sole´ JM, Hernandez JL, Carreras R. Feasibility of a new two-step procedure for office hysteroscopic resection of submucous myomas: results of a pilot study. Eur J Obstet Gynecol Reprod Biol. 2013;168:191–4.
51. Litta P, Vasile C, Merlin F, Pozzan C, Sacco G, Gravila P, Stelia C. A new technique of hysteroscopic myomectomy with enucleation in toto. J Am Ass Gynecol Laparoscop. 2003;10(2):263–70.
52. Saccardi C, Conte L, Fabris A, De Marchi F, Borghero A, Gizzo S, Litta P. Hysteroscopic enucleation in toto of submucous type 2 myomas: long-term follow-up in women affected by menorrhagia. J Minim Invasive Gynecol. 2014;21(3):426–30.
53. Mazzon I. Nuova tecnica per la miometomia isteroscopica: enucleazione con ansa fredda. In: Cittadini E, Perino A, Angiolillio M, Minelli L, editors. Testo-Atlante di Chirurgia Endoscopica Ginecologica. Palermo: COFESE Ed; 1995, cap XXXIIIb.
54. Mazzon I, Favilli A, Cocco P, Grasso M, Horvath S, Bini V, Di Renzo GC, Gerli S. Does cold loop hysteroscopic myomectomy reduce intrauterine adhesions? A retrospective study. Fertil Steril. 2014;101:294–8.
55. Bettocchi S, Ceci O, Di Venere R, et al. Advanced operative office hysteroscopy without anaesthesia: analysis of 501 cases treated with a 5 Fr bipolar electrode. Hum Reprod. 2002;17:2435–8.
56. Bradley LD. Complications in hysteroscopy: prevention, treatment and legal risk. Curr Opin Obstet Gynecol. 2002;14:409–15.
57. Vilos GA. Hysteroscopic surgery: Indication, contraindications and complications. London: Taylor & Francis; 2004.
58. Bahar R, Shimonovitz M, Benshushan A, Shushan A. Case–control study of complications associated with bipolar and monopolar hysteroscopic operations. J Minim Invasive Gynecol. 2013;20:376–80.
59. Van Kerkvoorde TC, Veersema S, Timmermans A. Long-term complications of office hysteroscopy: analysis of 1028 cases. J Minim Invasive Gynecol. 2012;19:494–7.
60. Arieff AI. Hyponatremia associated with permanent brain damage. Adv Intern Med. 1987;32:325–44.
61. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathyin menstruant women. Ann Intern Med. 1992;117:891–7.
62. Vilos GA, Brown S, Graham G, McCulloch S, Borg P. Genital tract electrical burns during hysteroscopic endometrial ablation: report of 13 cases in the United States and Canada. J Am Assoc Gynecol Laparosc. 2000;7:141–7.
63. Vilos GA, McCulloch S, Borg P, Zheng W, Denstedt J. Intended and stray radiofrequency electrical currents during resectoscopic surgery. J Am Assoc Gynecol Laparosc. 2000;7:55–63.
64. Munro MG. Mechanisms of thermal injury to the lower genital tract with radiofrequency resectoscopic surgery. J Minim Invasive Gynecol. 2006;13:36–42.
65. Giatras K, Berkeley AS, Noyes N, Licciardi F, Lolis D, Grifo JA. Fertility after hysteroscopic resection of submucous myomas. J Am Assoc Gynecol Laparosc. 1999;6:155–8.
66. Taskin O, Sadik S, Onoglu A, Gokdeniz R, Erturan E, Burak F, Wheeler J. Role of endometrial suppression on the frequency of intrauterine adhesions after resectoscopic surgery. J Am Assoc Gynecol Laparosc. 2000;7(3):351–4.
67. Yang J, Chen M, Wu MY, Chao KH, Ho HN, Yang YS. Office hysteroscopic early lysis of intrauterine adhesion after transcervical resection of multiple apposing submucous myomas. Fertil Steril. 2008;89:1254–9.
68. Cicinelli E. Hysteroscopy without anesthesia: review of recent literature. J Minim Invasive Gynecol. 2010;17:703–8.
69. Pellicano M, Guida M, Zullo F, Lavitola G, Cirillo D, Nappi C. Carbon dioxide versus normal saline as uterine distension medium for diagnostic vaginoscopic hysteroscopy in fertile patients: a prospective randomized, multicenter study. Fertil Steril. 2003;79:418–21.
70. Shankar M, Davidson A, Taub N, Habiba M. Randomized comparision of distension media for outpatient hysteroscopy. BJOG. 2004;111:57–62.
71. Cooper NA, Smith P, Khan KS, et al. Vaginoscopic approach to outpatient hysteroscopy: a systematic review of the effect on pain. BJOG. 2010;117:532–9.
72. Saridogan E, Tilden D, Sykes D, Davis N, Subramanian D. Cost-analysis comparison of outpatient see-and-treat hysteroscopy service with other hysteroscopy service models. J Minim Invasive Gynecol. 2010;17:518–25.
73. Lobo P, Rubio J, Cabrera Y, Duch S, Alvarez J. Economic analysis of outpatient versus day-case operative hysteroscopy. A progressive scenario model. Prog Obstet Ginecol. 2014;57(4):155–63.
74. Subramanian S, Clark MA, Isaacson K. Outcome and resource use associated with myomectomy. Obstet Gynecol. 2001;98:583–7.

Uterine Artery Embolization and New Ablation Techniques

10

Wouter J.K. Hehenkamp, Judith A.F. Huirne, and Hans A.M. Brölmann

Introduction

Only a few decades ago, the only surgical treatments to treat symptomatic uterine fibroids were an abdominal (sometimes vaginal) hysterectomy or abdominal myomectomy. Both are rather invasive procedures with relatively long recovery times. Firstly, hysteroscopic myomectomy became available for submucosal fibroids, as first described by Neuwirth and Amin in 1976 [1]. A new technique with many benefits such as a minimally invasive approach, quick recovery and good clinical results. Since then the technique has been rapidly altered in order to make it feasible for many all over the world with many procedures performed each day. However, not all fibroids can be removed by hysteroscopy and for many women hysterectomy or abdominal myomectomy was still the only surgical option.

In 1994 Ravina described a new application of a (somewhat) older technique: embolization of the uterine fibroids by Uterine Artery Embolization (UAE) [2]. The therapeutic effect is based on occlusion of both uterine arteries, thereby stopping the blood flow to the fibroids with subsequent necrosis, whereas the uterus remains relatively unaffected because of collateral blood supply through the ovarian arteries. This technique was initially meant as a pretreatment for myomectomy: decreasing the blood flow to the fibroids before surgery in order to decrease sometimes extensive blood loss and make them shrink to make surgery easier and less lengthy. It appeared however that symptoms were decreasing dramatically after UAE, resulting in patients cancelling their surgery. Afterwards Ravina reported a case series of 16 patients that underwent this new treatment as an alternative to major surgery such as hysterectomy or myomectomy [3]. Eleven out of sixteen patients had a good symptom improvement, three had partial improvement and two showed no improvement at all and required further surgical intervention. With this publication in the Lancet a new treatment modality was born, resulting in many case series, randomized controlled trials and registries. Nowadays, UAE is applied all over the world and has become a standard treatment option in uterine fibroid therapy.

Also other techniques have been introduced with another mechanism of action: uterine fibroid ablation. Ablation can be applied with a bipolar electrode (hysteroscopically or laparoscopically depending on the location of the fibroid) or through MRI guided focused ultrasound.

W.J.K. Hehenkamp, MD, PhD (✉)
J.A.F. Huirne, MD, PhD
H.A.M. Brölmann, MD, PhD
Department of Obstetrics and Gynaecology,
VU University Medical Center,
Amsterdam, The Netherlands
e-mail: w.hehenkamp@vumc.nl;
j.huirne@vumc.nl; h.brolmann@vumc.nl

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This chapter will discuss these new techniques, the indications to perform them, and the evidence on efficacy of Uterine Artery Embolization and the available ablation techniques.

Uterine Artery Embolization

The Procedure

UAE is mostly performed by interventional radiologists. The procedure takes place under local anesthesia (sometimes combined with epidural anesthesia for post-operative pain relief) by a trained interventional radiologist. UAE is a percutaneous angiographic procedure performed with video fluoroscopic imaging. A catheter is eventually placed in the uterine artery via the femoral artery (Fig. 10.1a). Diagnostic angiography of the artery is obtained to confirm proper position. Embolization is then performed using embolization material (Fig. 10.1b). Many embolic agents are available. Most commonly the following embolic agents are used: nonspherical polyvinyl alcohol (PVA); spherical PVA; acrylamido PVA; tris-acryl gelatin microspheres and polyzene-F hydrogel microspheres. No clear distinction can be made between the embolic materials in terms of effectivity. The large randomized trials [4–6] used mainly poly-vinyl alcohol particles, but all other materials are used in other studies. Recently a systematic review was published on this subject [7] describing 5 randomized and 5 non-randomized studies comparing one or more of these embolic agents. No clear superiority for one specific embolic agent could be identified. The embolic material is injected through the catheter and is carried by the arterial blood flow to the vessels feeding the fibroid. These vessels are preferentially occluded since they are larger and have a higher flow than normal myometrial branches. Besides this, there is collateral blood flow from the ovarian arteries. The procedure is usually terminated when the fibroid blood supply is occluded but there is still some flow in the uterine artery. The catheter is then moved to the ipsilateral internal ileac artery (sometimes by placing a catheter in the contralateral femoral artery), and the procedure is repeated in the opposite uterine artery [8, 9]. In Fig. 10.2 the angiographic image is demonstrated both before (**A**) and after (**B**) UAE. Figure 10.3 demonstrates an MRI scan of a uterus with fibroids prior to UAE (**A**) and 6 months after UAE (**B**).

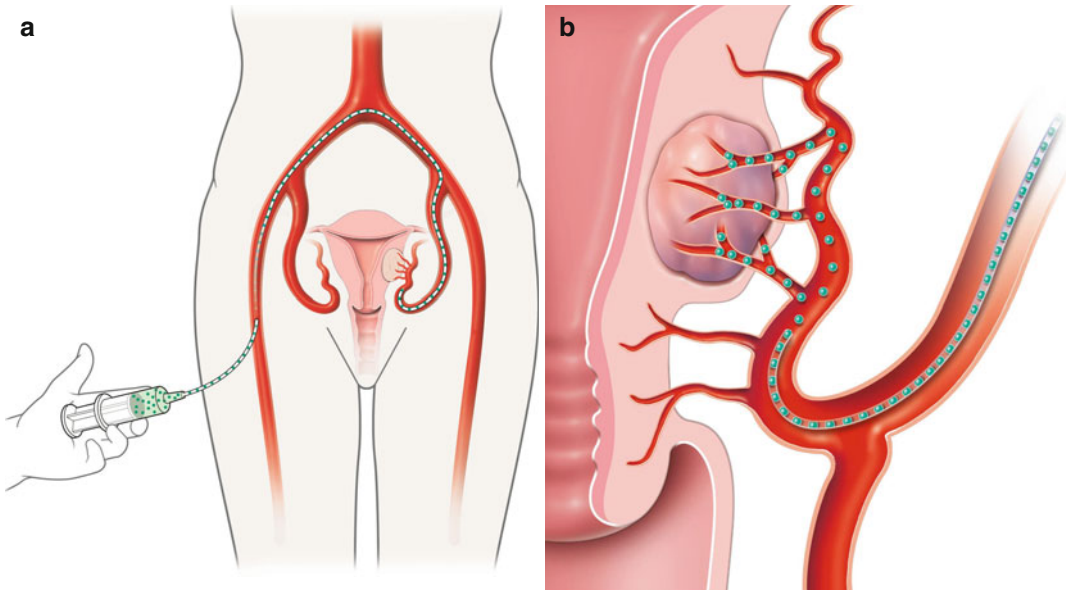

Fig. 10.1 (**a**) A catheter is placed in the uterine artery via the femoral artery (Copyright CeloNova Biosciences Inc.). (**b**) Detail of **a**. Small particles are injected in the uterine artery obstructing the vessels towards the fibroid (Copyright CeloNova Biosciences Inc.)

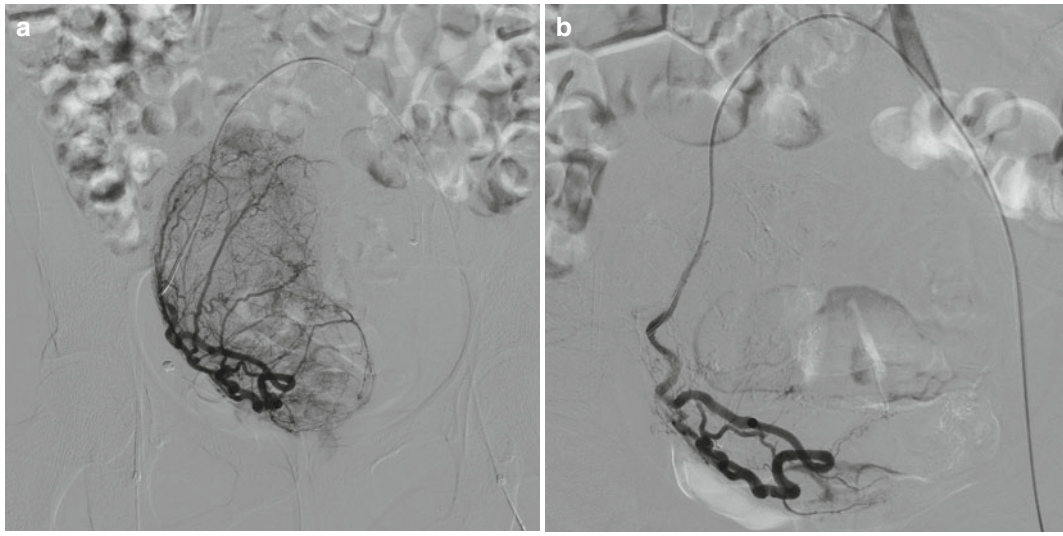

Fig. 10.2 (**a**) Pre-UAE angiogram. (**b**) Post-UAE angiogram: fibroid blush disappeared

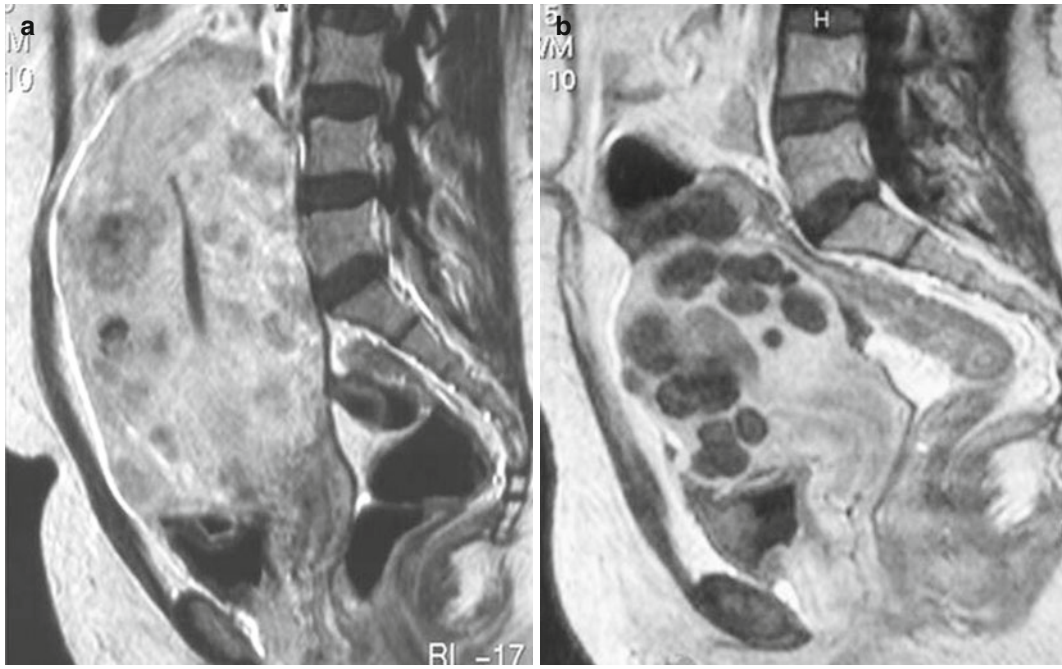

Fig. 10.3 (**a**) Sagittal MRI demonstrating uterus with fibroids prior to UAE. (**b**) MRI after UAE will follow later. Sagittal MRI demonstrating same uterus with fibroids from figure **a** 6 months after UAE

Patient Selection and Prediction of UAE Outcome

Several prognostic factors have been identified to predict effect of UAE on fibroid volume, complaints and need for re-interventions (Table 10.1). Three types of predictive factors can be identified: factors that can be established before UAE, during UAE and after UAE. Before UAE the vascularity of the fibroids, as established by contrast enhanced MRI, predicts outcome: hypervascular fibroids predict a long regrowth free interval [10].

Table 10.1 Predicting UAE outcome

	Factor	Outcome
A. Before UAE	Hypervascular fibroids on MRI	Long regrowth-free interval
	Submucosal location	Larger improvement QOL-score
	Smaller size of fibroid(s)	Larger improvement QOL-score
	Heavy menstrual bleeding as presenting symptom	Larger improvement QOL-score
	Larger size fibroid(s)	Higher chance of symptom recurrence, higher chance of failure
B. During UAE	Unilateral UAE	More secondary hysterectomies
C. After UAE	Less than 90 % infarction (MRI) of fibroids after UAE	More re-interventions
	Post-UAE Dopplers (resistance index)	Fibroid volume decrement
	No improvement of pain or bleeding at 1 year follow-up	More re-interventions
	More volume reduction	More satisfaction

UAE uterine artery embolization, *QOL* quality of life

Furthermore, a smaller leiomyoma size, a submucosal location of the fibroids, and heavy menstrual bleeding as the presenting symptom are predictors of a more significant fibroid related symptom change score [11]. Finally, larger fibroids and more numerous fibroids predict higher symptom recurrence and higher failure rates [12, 13]. During the procedure only a unilateral UAE predicts failure, defined as secondary hysterectomy [14]. Directly after the procedure the following factors were of predictive value: when less than 90 % of the fibroids showed signs of infarction on the post-UAE MRI scan there was more chance of re-interventions [15, 16]. Post-UAE fibroid volume at follow up was related to post-UAE dopplers (resistance index) directly after the procedure [17].

When there was no improvement in bleeding or pain at 1 year after UAE, this was indicative for failure [13, 18]. The percentage reduction in dominant tumor volume also predict failure, defined as need for re-intervention [18]. Finally, when volume reduction of fibroids was in the first tertile, patients more likely to be dissatisfied with outcome compared with women in the third tertile [13].

Although all these predictors have not been prospectively evaluated, the somewhat smaller and well vascularized fibroids seem to have the best results. Also it is important to ensure that the whole volume of the fibroid is embolized. Finally, when symptoms have not or only marginally improved after 1 year, the re-intervention rate seems to increase.

Being able to predict the outcome of UAE is very important in selecting patients for this procedure. Especially the first category (factors known before UAE) needs to be further explored, since this differentiates between patients that are good candidates for UAE and the group of patients that might be better off with another treatment.

Indications and Contra-Indications

Uterine Artery Embolization is indicated primarily for uterine fibroids. Another indication is severe post-partum hemorrhage as a last resort before a post-partum hysterectomy needs to be performed [19]. This procedure will not be discussed in this chapter. Although some literature is available on UAE for adenomyosis, the vast body of evidence concerns uterine fibroids. The evidence on UAE for symptomatic adenomyosis is summarized in a review by Popovic et al. [20]. In total 511 women have been reported in this review with a positive effect on symptoms for 75.7 % of patients. No randomized data are available on this topic: patients were treated by UAE

for adenomyosis without a control group. Since adenomyosis patients have no other option than radical surgery when conservative treatment fails, UAE could be an option. Randomized data are needed though for appropriate counseling on effectiveness and safety.

UAE for symptomatic fibroids has been performed for a variety of symptoms. Good results have been shown on associated heavy menstrual bleeding (HMB), dysmenorrhea and bulk-symptoms, although performing UAE only for the latter is questionable.

Absolute contraindications are considered to be: current pregnancy, presence of pelvic inflammatory disease, presence of uterine malignancy and asymptomatic fibroids.

Several relative contraindications have been proposed.

Narrow stalked (arguably when the stalk is <50 % of the largest diameter of the fibroid) pedunculated subserosal or submucosal fibroids are considered relative contraindications, since these might cause fibroid expulsion with concurrent intrauterine infection (submucosal fibroids) or sterile peritonitis due to detachment of fibroids (subserosal fibroids). Pedunculated fibroids are considered relatively contraindicated since it depends on the size (with very small fibroids most probably less of a problem than large ones), the possibility to subsequently remove the fibroids by hysteroscopy or laparoscopy.

Since there might be effect on ovarian reserve and uterine function UAE is usually not recommended as a standard treatment when a woman still wishes to get pregnant in the future (see also below). Another relative contraindication might be a very large uterus with multiple very large fibroids. The volume of necrosis can be substantive, with the related post-procedural pain and risk of infection. However, no clear cut-off can be given for size related to problems. No studies are available that provide evidence on a cut-off for size. There are several series though, that demonstrate good results even on very large uteri [21–24]. In these publications there appears to be no relation between the size of the uterus and post-embolization symptomatology or satisfaction. Also, failure rates defined as secondary hysterectomies were similar as in other series. Also volume reduction was similar to patients with smaller fibroids, although a large volume was still present after the procedure because of a large volume before UAE.

The procedure is indicated primarily for premenopausal women, since fibroids tend to decrease in size and symptoms after menopause. A growing uterus after menopause should raise the suspicion of a malignancy and careful imaging and follow up is warranted in that case.

Pre-procedural Imaging and Workup

Most protocols agree on the need of MRI before UAE in order to properly diagnose uterine fibroids. In our view, in many cases an MRI can be prevented, when ultrasound provides a clear diagnosis and can locate fibroids according to the international classification system [25]. It has been shown that –in expert hands- ultrasound is as reliable in detecting fibroids as MRI scan [26]. However, when multiple fibroids are present of fibroids are very big, MRI is superior. Therefore, when ultrasound is inconclusive, no expert is available, or the uterus is too large to screen reliably by ultrasound, MRI is a very good and reliable tool to diagnose uterine fibroids and their location in the uterus.

When HMB is present hemoglobin testing is mandatory. Renal clearance should be tested (GFR) since contrast fluid is used.

Policy on prophylactic antibiotics varies among clinics and in publications on UAE. On average post-embolization infection prevalence is estimated to be 2 %. No randomized trials have been done to establish the value of antibiotics in UAE. Pathophysiologically infection seems to be more likely longer after UAE since bacteria might grow easier in necrotic tissue.

Thromboprofylaxis in general is only applicable for intravascular procedures when a patient is at increased risk for thromboembolic disease [27].

Complications After UAE

Since severe complications in general are usually rare in elective surgery, large series are necessary to identify true complication rates. Therefore, randomized controlled trials (with usually relatively few patients) seldom have complications as a primary outcome and are not exclusively suitable for research on complication rates. Furthermore, complications are assessed using different complication classification systems making comparisons difficult.

Mortality after UAE is extremely rare, but several case-reports have been written [28–32]. Causes of death were septicemia (n = 2), pulmonary embolus (n = 2) and systemic non-target embolization in a woman with arteriovenous shunting and patent foramen ovale.

In a national registry in the United States (n = 3,160) major complications (as defined by the Society of Interventional Radiology Clinical Practice Guidelines) were reported in 0.66 % of patients in the initial hospitalization period and in 4.8 % during the first month after discharge [33]. A large systematic review has been done in 2012 on complications after UAE yielding several specific numbers for specific complications [34]. In this review 54 studies were summarized with a total of 8,159 patients. Major complications occurred in 2.9 % of patients. The rate of hysterectomy for resolution of a complication from UAE was 0.7 %, and the rate of readmission was 2.7 %.

Morbidity after UAE can also be divided in peri-procedural, early complications and late complications (beyond 30 days).

Peri-procedural complications include groin hematoma, arterial thrombosis and (pseudo) aneurysm and are uncommon [35, 36]. Bilateral failure of UAE is also considered a complication and occurs in 4 % of all patients that had their UAE in a clinical trial [36].

Early complications that often occur are fever, nausea, pain and malaise and form the 'post-embolization syndrome' [35]. This is usually self-limiting and can be managed with non-steroid- anti-inflammatory drugs [37]. When these symptoms persist or get worse, re-admission might be necessary (up to 9 % of cases) [35]. Compared to hysterectomy/myomectomy more readmissions were seen after UAE because of these complications [38]. Serious early complications are deep venous thrombosis or pulmonary embolism, with an incidence of 0.2 % [34].

Late complications (beyond 30 days) comprise vaginal discharge, fibroid (tissue expulsion) and amenorrhoea (see below). Vaginal discharge Another complication that is also relatively common (16–20 %) is vaginal discharge [34]. This can last for months, and is also self-limiting, provided that the discharge is not purulent and fever is absent (otherwise there might be a need to start treatment with antibiotics). Expulsion of a fibroid (or fibroid tissue) is a relatively common phenomenon and can generable be awaited, but sometimes it can be necessary to perform a hysteroscopy [39]. Fibroid tissue expulsion has been recorded in 4.7 % of patients [34].

Endometritis occurs in 0.5 % of cases (mostly submucosal fibroids) and responds well to antibiotics (a culture should be performed) [39]. In case of persistent discharge combined with abdominal tenderness or pain, it is possible that a necrotic fibroid is being expelled.

Effect on Ovarian Function

Amenorrhoea is an unintended sign, the cause of which is still largely unknown. Arterial flow to the ovary is likely to be transiently occluded during UAE, but may be reestablished on the longer term [40]. The overall incidence of permanent amenorrhoea is 3.9 % [34]. In women older than 45 years of age, there is a significantly higher risk of a decrease in ovarian reserve as detected by an FSH assay compared with younger women, as well as a higher risk of treatment-induced menopausal symptoms and/or amenorrhea. At this time, current data suggest that UAE for women younger than 40 years of age is unlikely to decrease ovarian reserve since no differences were found in any of the ovarian reserve parameters after treatment compared to before treatment [40]. One RCT evaluated Anti-

Mullerian-Hormone (AMH) levels in UAE patients compared to hysterectomy patients before and after the procedure [41]. AMH was significantly decreased in both groups compared to baseline but recovered in the hysterectomy group, whereas the AMH levels stayed significantly below the expected decrement in UAE patients, indicating at least some damage to the ovaries after UAE. The average age of patients was >45 years though. The effect on fertility remains uncertain (see also below).

Management of Complications

Good counseling is important for several complications such as prolonged discharge or loss of fibroid tissue and the post-embolization-syndrome. Should there be a persistent high fever, further workup is obligatory. Investigations include physical and vaginal examination including vital signs and swabs of discharge if present, blood examination and ultrasound examination of the uterus [39]. Post-embolization necrosis of the fibroid can give high pain-scores [42]. Treatment lies in the first place in giving adequate pain medication, unless pain seems to originate in fibroid expulsion, infection or non-target embolization. If the work-up demonstrates an infection, it is recommended to start intravenous antibiotics.

Outcome of UAE

UAE is mostly indicated for heavy menstrual bleeding, although it is also applied for dysmenorrhea, pelvic pain or pressure symptoms. Regarding the effect of UAE on heavy menstrual bleeding (HMB), it has been shown that most patients (73–90 %) reported improvement or disappearance of symptoms up to 5 years after treatment [43].

Most trials however, did not report on improved HMB but rather on satisfaction with treatment. A recently published Cochrane review on long-term results of UAE versus surgery chose satisfaction as the primary outcome measure, and showed that UAE had a similarly high satisfaction-rate as myomectomy and hysterectomy [38].

Quality of life was consistently better after UAE compared to baseline and comparable to surgical alternatives [5, 6]. Quality of life results were summarized in a systematic review comparing UAE with surgery, showing that health related quality of life was, even after 5 years of follow up, significantly higher than baseline without any differences between the studied groups [35]. The effect of UAE on bulk and pressure-complaints is less well studied, but in large cohort studies up to 90 % of patients reported improved bulk-complaints [44, 45]. The effect of UAE on lower abdominal pain or dysmenorrhea has also been described and shows an improvement in up to 80 % of patients [46]. Since pain-and bulk complaints were not investigated in validated questionnaires it is not possible to present quantitative outcomes.

Secondary interventions after UAE for failure or recurrence of symptoms have been reported to be 27 % (51/187) in the RCTs at 5 years of follow up [35]. The case series and registries report higher success rates (80–90 %) [13, 47].

Another important benefit of UAE is a significantly shorter hospital stay, and a significantly faster resumption of daily activities and work [38].

UAE and Fertility

As stated before, an important relative contraindication is the wish to conceive. Since hysterectomy is obviously impossible in this case, a myomectomy used to be the gold standard. UAE is increasingly applied in this group of patients with reassuring results. However, good comparative data are lacking. The effect of UAE on (sub) fertility has not been well investigated. There is evidence on the adverse effect of fibroids on fertility. It is known that submucosal and intramural fibroids might have a negative impact on fertility, however, this does not automatically mean that treatment of the fibroids will improve fertility outcomes. Subserosal fibroids do not appear to

have a significant effect on fertility outcomes. For intramural fibroids this is not known [48].

If (sub)fertility is likely to be caused by the presence of fibroids, it may be considered to embolize them. In a systematic review on pregnancies after UAE it was stated that miscarriage rates were higher in post-UAE pregnancies (35.2 %) compared with pregnant women with a non-treated fibroid-uterus (16.5 %), matched for age and fibroid location. The UAE pregnancies were more likely to be delivered by cesarean section and to experience post partum hemorrhage. Rates of preterm delivery, intra uterine growth restriction and malpresentation were similar in UAE pregnancies and in control pregnancies with fibroids [49]. In the recently published Cochrane review that was mentioned earlier, the other primary outcome measure was live birth rate. This was calculated from the limited cohort of participants who tried to conceive in the study of UAE versus myomectomy. There was no significant difference between the groups in live birth rate [50]. On the basis of these results myomectomy should be regarded as the gold standard. UAE in women with a child wish should ideally be performed in research setting and/or after appropriate counseling.

Follow Up After UAE

After discharge the patient should be aware of the risk of minor and major complications (see above) and should know how to detect them. In case of increasing pain, fever, foul smelling discharge the patient should contact her specialist in order to rule out complications.

Although all trials report on imaging follow up, in daily clinical practice the patient and her complaints should be leading in considering post-procedural imaging and labwork. Good response in terms of volume reduction but unchanged HMB might result in re-intervention, whereas the opposite situation might not. In that perspective imaging does not add to follow up, unless it is for research purposes. When HMB persists, hemoglobin checkups are necessary for iron-supplement indication.

The Future of UAE

Although extensive research has been done on this topic, several aspects remain unanswered or can be optimized. UAE has not properly been compared to another common uterus sparing technique: surgical myomectomy. In this perspective: good randomized data on future fertility is needed in order to establish the role of UAE in patients with a wish to conceive. Several initiatives have been taken in this perspective: The FEMME trial (ISRCTN70772394) randomizes patients with fibroids with the wish to preserve their uterus between UAE and myomectomy. The FEMME trial is still in the recruitment process. The FIRSTT-trial (NCT00995878) compares UAE to HIFUS and is expected to finish data-collection in 2015. A similar trial is currently performed with an estimated end-date of may 2014 (NCT01834703). Next to evaluation of UAE, selection of patients can be elucidated somewhat further. Prognostic factors such as vascularity for a successful procedure can be investigated more clearly and consistently.

Even though some questions remain unanswered, many have been answered placing UAE consistently among the various possibilities for fibroid therapy.

New Fibroid Ablation Techniques

Radiofrequency Ablation (RFA)

RFA in general refers to the destruction of tissue by focused energy with electric current through a bipolar electrode or a monopolar electrode, by radiofrequency or by a cryoprobe used as energy sources.

RFA was introduced in the late 1980s in Europe as a conservative treatment of uterine fibroids [51]. At first, it was performed with the use of the ‘Neodynium: Yttrium Aluminium Garnet’ (Nd:YAG) laser. Later, bipolar needles were developed as an alternative to this laser option (this technique was called ‘myolysis’). The technique was further refined and is nowadays performed under sonographic guidance

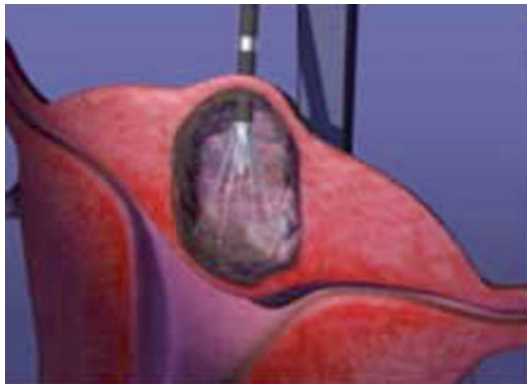

Fig. 10.4 Laparoscopically, the Handpiece tip is advanced into the fibroid with ultrasound guidance (Source: www.haltmedical.com)

(radiofrequency volumetric thermal ablation, RFVTA). These techniques can be performed laparoscopically (Fig. 10.4) or transcervically (Fig. 10.5). In the newer transcervical devices the ultrasound probe is built in.

Laparoscopic RFA

Recently one RCT has been published comparing laparoscopic RFA with laparoscopic myomectomy [52]. Although a 5 year follow up period was planned with outcomes such as pregnancy outcome after RFA, symptom improvement, re-intervention rates and recurrence of fibroids, this first publication describes short term outcomes only. In total 51 patients were randomized between RFA and laparoscopic myomectomy. RFA was significantly better in terms of mean hospitalization time (10 versus 30 h), operative blood loss (16 versus 51 ml). Not significantly different were mean number of excised fibroids per patient (2.8 versus 2.0), operation time (1.1 h versus 1.3 h). No major complications or conversions occurred.

Several prospective studies have been published. Garza Leal et al. published a prospective study with 31 patients that underwent laparoscopic RFA for symptomatic fibroids, where fibroid symptoms and volumes were successfully reduced. At 3, 6, and 12 months, mean symptom severity score improved significantly compared with baseline: by 59.7, 71.7, and 82.0 % respectively. The increase in mean health related quality of life scores over time was statistically significant ($p<0.001$): 60 at baseline and 98 at 12 months. Mean uterine volume decreased from 194.4 (standard deviation: 105.9 cm^3) at baseline to 113.2 (standard deviation 53.5 cm^3) at 12 months ($p=0.006$) [53].

In the HALT trial 135 patients were followed up after laparoscopic RFA [54]. Of these, 104 subjects followed through 36 months of follow up. They reported a continued improvement of symptom severity, quality of life, and health-state scores. The overall re-intervention rate at 36 months was 10.4 %. RFA of uterine fibroids resulted in sustained and significant relief form fibroid symptoms and significant continued improvement in health-related quality of life to 36 months post-ablation. These data make this new technique promising, but good randomized data on long term follow up and efficacy is needed. A randomized trial has been registered in this perspective (the TRUST study, NCT01563783) comparing RFA with myomectomy in women with a desire for future pregnancy and RFA with Uterine Artery Embolization in women without future fertility wish (estimated end date December 2019).

Trans-Cervical RFA

No RCTs have been published on trans-cervical Radio Frequency Ablation yet. Recently, a prospective cohort-study using transvaginal ultrasound-guided RFA was performed in 69 premenopausal women with symptomatic uterine fibroids as an outpatient procedure [55]. Mean baseline volume of the dominant fibroids was 304.6 cm^3 and its volume at 3 months following radiofrequency myolysis decreased significantly ($p=0.002$). An improvement of heavy menstrual bleeding occurred 1, 3, 6 and 12 months after operation (all $p<0.001$ versus baseline). No major complications were observed or reported. After 12 months, three patients had successfully conceived and delivered and there were no complications during labor or delivery. The technique was further refined, and a intrauterine ultrasound probe was developed attached to the ablation device. The first experiences of this new device were reported in a small cohort of 19 patients with 20 fibroids that would undergo a hysterectomy for

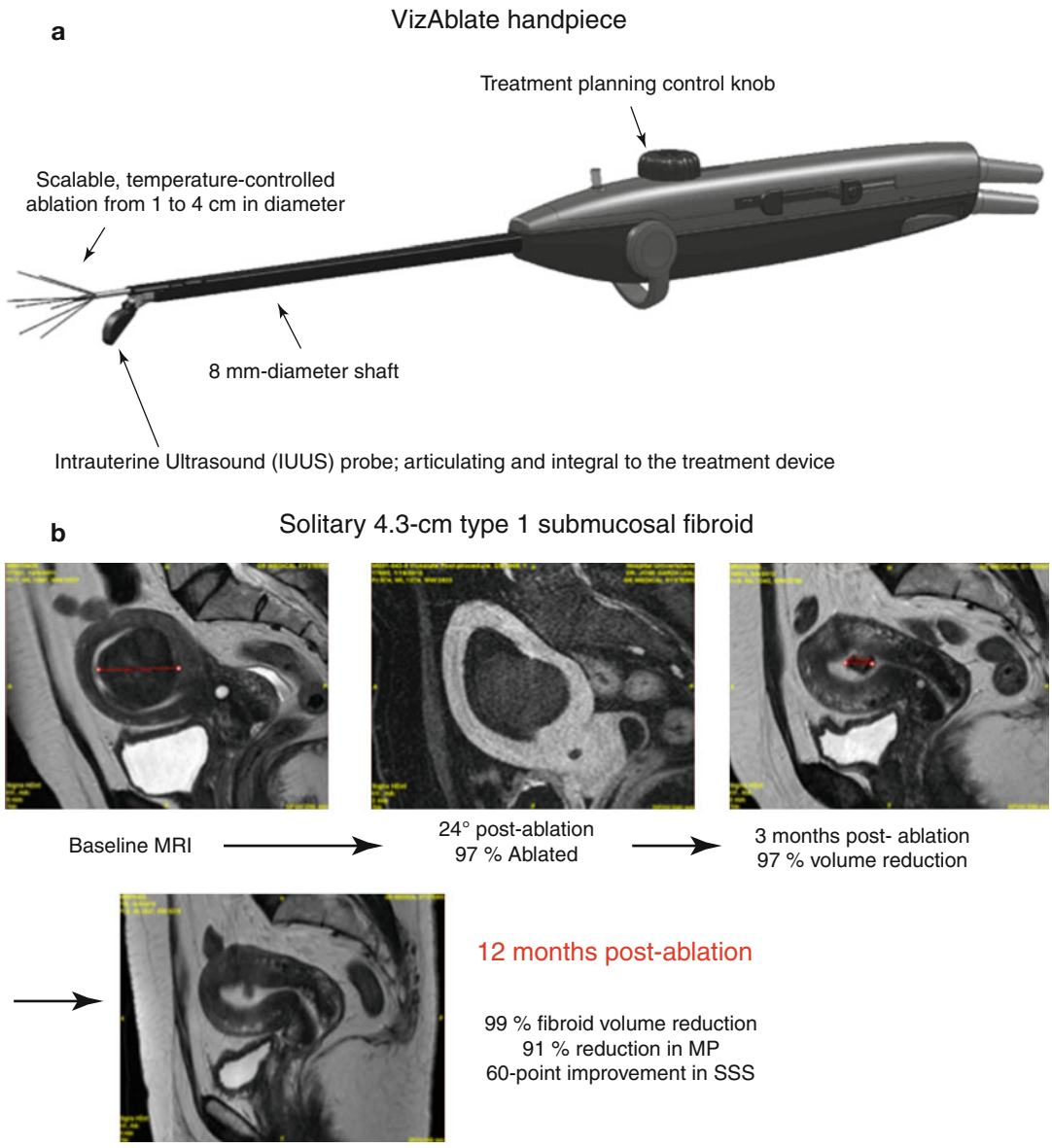

Fig. 10.5 (**a**) Placement of bipolar needles in fibroid in order to do trans-cervical ablation. The ultrasound probe is directed downwards right before the surface of the fibroid (Source: Gynesonics Inc.). (**b**) MRI with contrast of uterus with single fibroid. On the *left image* the situation prior to ablation is visible. On the *right side* the MRI is repeated demonstrating no flow in the fibroid anymore (Source: Gynesonics Inc)

symptomatic uterine fibroids in the next weeks. Directly after surgery the extend of ablation was investigated: 67 % (± 27 %) of the fibroid volume was successfully ablated [56]. Currently this device is tested for symptomatic relief and feasibility. Pregnancy outcomes after RFA have only been described anecdotally in case-reports.

MRI Guided High Intensity Focused Ultrasound

High Intensity Focused Ultrasound (HIFU) is a relatively new technique for the treatment of symptomatic uterine fibroids, which uses heat generated by high-intensity focused ultrasound in

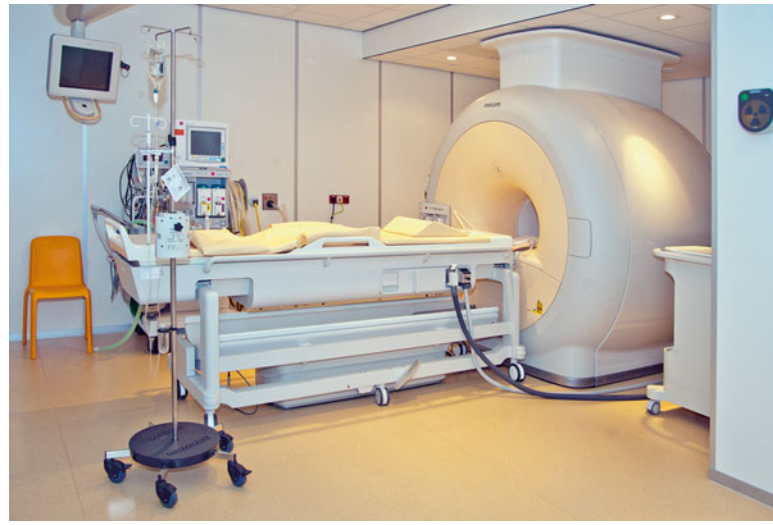

Fig. 10.6 Clinical Sonalleve MR-HIFU platform (From Ikink et al. [58])

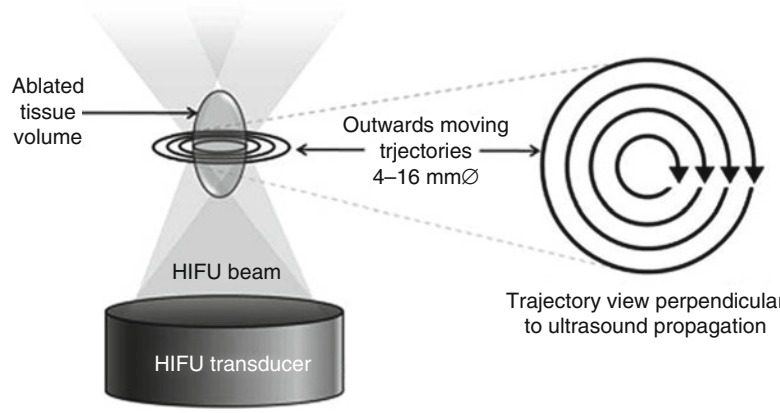

Fig. 10.7 Schematic representation of the volumetric ablation trajectory. The electrically-steered acoustic focus is moved along concentric circular subtrajectories on a plane perpendicular to the HIFU beam producing an ellipsoidal thermal volume (diameter = 4, 8, 12 or 16 mm) (From Voogt et al. [59])

order to destruct tissue. Magnetic Resonance Imaging (MRI) is used for planning and real-time monitoring of the treatment. Therefore this treatment is also referred to as MRI guided focused ultrasound (abbreviated as MRgFUS or MR-HIFU). The same technique can be applied under sonographic guidance [57], although very little literature is available on this technique. MRI guidance is much more common. Therefore, literature description in this paragraph is only based on MRI guided HIFU (briefly HIFU, see Figs. 10.6 and 10.7).

The advantages of HIFU is its completely non-invasive character, which makes it a unique treatment option for patients with fibroids. Furthermore, continuous imaging of fibroids and adjacent structures is possible, which optimizes fibroid ablation and prevents injury to adjacent tissues [60]. The disadvantage is that relatively few patients are eligible, i.e. only those with fibroids located immediately beneath the anterior abdominal wall without bowel interposition or scars in the region of interest, and that average treatment time is long [59]. Interestingly, several studies report that highly vascularized fibroids are less suitable for HIFU, possibly because of transportation of the heat by blood flow in highly vascularized lesions. Two studies reported that only 16–25 % of referred patients were eligible for HIFU treatment [61, 62]. No RCTs have been published yet, therefore evidence comes from retrospective or prospective studies. In a

prospective study with 33 patients with intravenous fentanyl the reported average pain score (VAS 1–10) was 1.8 ± 2.6 during treatment, with a statistically insignificant increase in pain scores to 2.4 ± 2.6, 24 h post-treatment [59]. A prospective study with 40 patients showed mean improvement scores for symptom severity scale (SSS, 1–100) of −47.8 and for UFS-QOL (Uterine Fibroid Symptom and Quality of Life questionnaires, scale 1–100) of 39.8 at 3 years. The mean volume decrease in treated fibroids was 32.0 %, and the volume decrease of the whole uterus was 27.7 % at 3 years [63]. Another cohort evaluated 46 women with 58 symptomatic fibroids. The mean volume reduction of the fibroids was 29 %. Clinical follow-up showed that 25 of the 46 patients reported a more than 10-point reduction in the SSS. Among 130 patients treated with HIFU, complications were observed in a retrospective analysis. One major complication occurred: a deep vein thrombosis. Minor complications were more common: abdominal edema/erythema in 11 patients and lower back discomfort in 5 patients [64]. A prospective registry of all known pregnancies occurring after HIFU reported on 51 women with uterine fibroids [65]. The mean age of the women at the time of treatment was 37.2 ± 4.6 years. The spontaneous miscarriage rate was 26 %, which is comparable to the rate in women of similar age without fibroids [66]. Live births occurred in 41 % of pregnancies, with an 11 % rate of elective pregnancy termination, and 20 % ongoing pregnancies beyond 20 gestational weeks the moment the study ended. The vaginal delivery rate was 64 %.

Although HIFUS is a complex technology and the initial set-up is expensive, the extensive improvement in quality of life makes that it rapidly becomes cost-effective over a relatively short period of time. In a model, the incremental cost of an HIFU treatment strategy compared with current treatment, resulted in a cost saving of £295 per patient [67].

At present, only a minority of women with uterine fibroids seems to meet the inclusion criteria for this new technique. An issue that is extensively reviewed in a recent overview of manipulating techniques to overcome several contra-indications [68]. An example as addressed in this review is the filling of the bladder in order to change the position of the uterus and therewith overcoming interposition of bowel. However, in the lack of randomized data, HIFU should still be regarded as an experimental treatment. As reported previously, two trials are recruiting patients (NCT00995878 and NCT01834703) that compare HIFU to Uterine Artery Embolization. When these trials have been published recommendations can possibly be made.

Conclusion

Minimally invasive treatments for uterine fibroids such as Uterine Artery Embolization, High-Intensity-Focused-Ultrasound and fibroid ablation are becoming increasingly popular, as illustrated by several initiatives to develop and evaluate these alternatives and the growing body of evidence on these techniques. Especially UAE has been evaluated extensively and has become a widely accepted standard for fibroid therapy. Patients can be well informed about this option and can weigh the risks and benefits carefully compared to surgical alternatives such as hysterectomy or myomectomy (Table 10.2). Nevertheless, women that wish to conceive in the future should be informed that UAE is not the treatment of first choice. When UAE is performed in these patients, they should be well aware of the possible side-effects and influence on pregnancy outcome. However, this is still not completely clear, allowing room for additional research in this group of patients.

The ablation techniques are newer, and still ‘under research’. Since there are no good and large randomized comparisons available no comparison can be made with other treatments. The prospective results are very promising though, making these treatment options interesting for further and future research.

Also, further research should focus on identifying favorable patient characteristics for the different minimally invasive approaches, such as vascularization, size and position of the fibroids in the uterus.

Table 10.2 Comparison of different minimally invasive fibroid therapies

	Uterine artery embolization	High Intensity Focused Ultrasound	Laparoscopic radiofrequency ablation	Transcervical radiofrequency ablation
Current status	Established	Experimental	Experimental	Experimental
Performed by	Interventional radiologist	Radiologist	Gynecologist	Gynecologist
Anesthesia	Local	No	General anesthesia	General/spinal anesthesia
Indications	Intramural fibroids (type 1–6) Heavy menstrual bleeding pain and bulk complaints	Fibroids anterior wall uterus Symptomatic fibroids	Fibroids <10 cm Fibroids Type 2 or more Uterus until 16 weeks size	Symptomatic fibroids adjacent to cavity (type 1/2/3)
Contraindications	Desire for fertility Narrow stalked fibroids (type 0/ type 7) Fibroids without vascularization	Desire for fertility Bowel interposition Lower abdominal scars Highly vascularized fibroids Deep fibroids Many fibroids	Desire for fertility Submucosal fibroids Contraindication laparoscopy Extensive abdominal adhesions	Desire for fertility Subserosal fibroids (>type 4) Large fibroids >10 cm
Results	QOL increases compared to baseline and similarly as hysterectomy Faster recovery than surgery Secondary procedures: 27 %	No comparison to other treatment Majority improved QOL compared to baseline	Discharge from hospital faster than myomectomy Improvement of symptom severity score compared to baseline	No comparison to other treatment Improvement heavy menstrual bleeding compared to baseline
Volume reduction fibroid	Around 50 %	Around 30 %	Around 40 %	unknown
Effect on fertility/ pregnancy outcome	Possibly decreased fertility Many cases described without problems Less favorable than myomectomy	No comparisons available Around 50 pregnancies described	No comparisons available Pregnancy described anecdotally	No comparisons available Pregnancy described anecdotally

QOL quality of life

References

1. Neuwirth RS, Amin HK. Excision of submucus fibroids with hysteroscopic control. Am J Obstet Gynecol. 1976;126:95–9.
2. Ravina JH, Merland JJ, Herbreteau D, Houdart E, Bouret JM, Madelenat P. Preoperative embolization of uterine fibroma. Preliminary results (10 cases) article in french. Presse Med. 1994;23(33):1540.
3. Ravina JH, Herbreteau D, Ciaru-Vigneron N, et al. Arterial embolization to treat uterine myomata. Lancet. 1995;346:671–2.
4. Volkers NA, Hehenkamp WJK, Birnie E, Ankum WA, Reekers JA. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: 2 years' outcome from the randomized EMMY trial. Am J Obstet Gynaecol. 2007;196:519 e1–e11.
5. Hehenkamp WJK, Volkers NA, Birnie E, Reekers JA, Ankum WA. Symptomatic uterine fibroids: treatment with Uterine Artery Embolization or Hysterectomy—results from the randomized clinical embolization versus hysterectomy (EMMY) trial. Radiology. 2008;246:823–32.
6. Edwards RD, Moss JG, Lumsden MA, Wu O, et al. Uterine artery embolization versus surgery for symptomatic uterine fibroids—the REST investigators. N Engl J Med. 2007;356:360–670.
7. Das R, Champaneria R, Daniels JP, Belli AM. Comparison of embolic agents used in Uterine Artery Embolisation: a systematic review and Meta-Analysis. Cardiovasc Intervent Radiol. 2014; Oct;37(5): 1179–90.
8. Goodwin SC, Spies JB. Uterine fibroid embolization. N Engl J Med. 2009;361(7):690–7.
9. Costatino M, Lee J, McCullough M, Nsouli-Maktabi H, Spies JB. Bilateral versus unilateral femoral access for uterine artery embolization: results of a randomized comparative trial. J Vasc Interv Radiol. 2010; 21(6):829–35.
10. Isonishi S, Coleman RL, Hirama M, Iida Y, Kitai S, Nagase M, Ochiai K. Analysis of prognostic factors for patients with leiomyoma treated with uterine arterial embolization. Am J Obstet Gynecol. 2008;198(3): 270.
11. Spies JB, Myers ER, Worthington-Kirsch R, Mulgund J, Goodwin S, Mauro M, FIBROID Registry Investigators. The FIBROID registry: symptom and quality-of-life status 1 year after therapy. Obstet Gynecol. 2005;106(6):1309–18.
12. Marret H, Cottier JP, Alonso AM, Giraudeau B, Body G, Herbreteau D. Predictive factors for fibroids recurrence after uterine artery embolisation. BJOG. 2005;112(4):461–5.
13. Spies JB, Bruno J, Czeyda-Pommersheim F, Magee ST, Ascher SA, Jha RC. Long-term outcome of uterine artery embolization of leiomyomata. Obstet Gynecol. 2005;106(5 Pt 1):933–9.
14. Gabriel-Cox K, Jacobson GF, Armstrong MA, Hung YY, Learman LA. Predictors of hysterectomy after uterine artery embolization for leiomyoma. Am J Obstet Gynecol. 2007;196(6):588.
15. Scheurig-Muenkler C, Koesters C, Grieser C, Hamm B, Kroencke TJ. Treatment failure after uterine artery embolization: prospective cohort study with multifactorial analysis of possible predictors of long-term outcome. Eur J Radiol. 2012;81(5):e727–31.
16. Kroencke TJ, Scheurig C, Poellinger A, Gronewold M, Hamm B. Uterine artery embolization for leiomyomas: percentage of infarction predicts clinical outcome. Radiology. 2010;255(3):834–41.
17. Naguib NN, Nour-Eldin NE, Serag-Eldin F, Mazloum YZ, Agameya AF, Abou-Seif S, Etaby AN, Lehnert T, Gruber-Rouh T, Zangos S, Ackermann H, Vogl TJ. Role of uterine artery Doppler in the management of uterine leiomyoma by arterial embolization. Ultrasound Obstet Gynecol. 2012;40(4): 452–8.
18. Lohle PN, Voogt MJ, De Vries J, Smeets AJ, Vervest HA, Lampmann LE, Boekkooi PF. Long-term outcome of uterine artery embolization for symptomatic uterine leiomyomas. J Vasc Interv Radiol. 2008; 19(3):319–26.
19. Kirby JM, Kachura JR, Rajan DK, Sniderman KW, Simons ME, Windrim RC, Kingdom JC. Arterial embolization for primary postpartum hemorrhage. J Vasc Interv Radiol. 2009;20(8):1036–45.
20. Popovic M, Puchner S, Berzaczy D, Lammer J, Bucek RA. Uterine artery embolization for the treatment of adenomyosis: a review. J Vasc Interv Radiol. 2011;22(7):901–9.
21. Prollius A, de Vries C, Loggenberg E, du Plessis A, Nel M, Wessels PH. Uterine artery embolisation for symptomatic fibroids: the effect of the large uterus on outcome. BJOG. 2004;111(3):239–42.
22. Smeets AJ, Nijenhuis RJ, van Rooij WJ, Weimar EAM, Boekkooi PF, Lampmann LE, Vervest HA, Lohle PN. Uterine artery embolization in patients with a large fibroid burden: long-term clinical and MR follow-up. Cardiovasc Intervent Radiol. 2010;33(5): 943–8.
23. Parthipun AA, Taylor J, Manyonda I, Belli AM. Does size really matter? Analysis of the effect of large fibroids and uterine volumes on complication rates of uterine artery embolisation. Cardiovasc Intervent Radiol. 2010;33(5):955–9.
24. Choi HJ, Jeon GS, Kim MD, Lee JT, Yoon JH. Is uterine artery embolization for patients with large myomas safe and effective? A retrospective comparative study in 323 patients. J Vasc Interv Radiol. 2013;24(6):772–8.
25. Munro MG, Critchley HO, Fraser IS, FIGO Menstrual Disorders Working Group. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertil Steril. 2011;95(7):2204–8.
26. Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Accuracy of MRI and transvaginal

ultrasonography in the diagnosis, mapping and measurement of uterine myomas. Am J Obstet Gynecol. 2002;186(3):409–15.
27. NICE guideline 2010. https://www.nice.org.uk/guidance/ipg367
28. De Blok S, de Vries C, Prinssen HM, Blaauwgeers HL, Jorna-Meijer LB. Fatal sepsis after uterine artery embolization with microspheres. J Vasc Interv Radiol. 2003;14:779–83.
29. Vashisht A, Studd J, Carey A, Burn PF. Fatal septicaemia after fibroid embolisation. Lancet. 1999;354: 307–8.
30. Brown KT. Fatal pulmonary complications after arterial embolization with 40–120-micro m tris-acryl gelatin microspheres. J Vasc Interv Radiol. 2004;15: 197–200.
31. Czeyda-Pommersheim F, Magee ST, Cooper C, Hahn WY, Spies JB. Venous thromboembolism after uterine fibroid embolization. Cardiovasc Intervent Radiol. 2006;29:1136–40.
32. Anonymous. Fatal nontarget embolization via an intrafibroid arterial venous fistula during uterine fibroid embolization. J Vasc Interv Radiol 2009;20(3): 419–20. doi:10.1016/j.jvir.2008.12.412. Epub 2009 Jan 23.
33. Worthington-Kirsh RL, Spies JB, Meyers ER. The Fibroid Registry for Outcomes data (FIBROID) for uterine embolization: short-term results. Obstet Gynecol. 2005;106(1):52–9.
34. Toor SS, Jaberi A, Macdonald DB, McInnes MD, Schweitzer ME, Rasuli P. Complication rates and effectiveness of uterine artery embolization in the treatment of symptomatic leiomyomas: a systematic review and meta-analysis. AJR Am J Roentgenol. 2012 Nov;199(5):1153–63.
35. Van der Kooij SM, Bipat S, Hehenkamp WJ, Ankum WM, Reekers JA. Uterine artery embolization versus surgery in the treatment of symptomatic fibroids: a systematic review and metaanalysis. AmJ Obstet Gynecol. 2011;205(4):e1–18.
36. Martin J, Bhanot K, Athreya S. Complications and reinterventions in uterine artery embolization for symptomatic uterine fibroids: a literature review and meta analysis. Cardiovasc Interv Radiol. 2013;36(2): 395–402.
37. Spencer EB, Stratil P, Mizones H. Clinical and periprocedural pain management for uterine artery embolization. Semin Interv Radiol. 2013;30(4): 354–63.
38. Gupta JK, Sinha A, Lumsden M, Hickey M. Uterine artery embolization for symptomatic uterine fibroids (Review). Cochrane Database Syst Rev. 2012;16(5): CD005073.
39. The Royal College of Obstetricians and Gynaecologists and the Royal College of Radiologists. Clinical recommendations on the use of uterine artery embolization (UAE) in the management of fibroids, third edition. London: RCOG and RCR, 2013. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/uterine-artery-embolisation-in-the-management-of-fibroids/
40. Kaump GR, Spies JB. The impact of uterine artery embolization on ovarian function. J Vasc Interv Radiol. 2013;24(4):459–67.
41. Hehenkamp WJK, Volkers NA, Broekmans FJ, de Jong FH, Themmen AP, Birnie E, Reekers JA, Ankum WM. Loss of ovarian reserve after uterine artery embolization: a randomized comparison with hysterectomy. Hum Reprod. 2007;22(7):1996–2005.
42. Hehenkamp WJK, Volkers NA, Birnie E, Reekers JA, Ankum WA. Pain and return to daily activities after uterine artery embolization and hysterectomy in the treatment of symptomatic uterine fibroids: results from the randomized EMMY trial. Cardiovasc Intervent Radiol. 2006;29:179–87.
43. Spies JB. Current evidence on uterine embolization for fibroids. Semin Interv Radiol. 2013;30:340–6.
44. Spies JB, Ascher SA, Roth AR, Kim J, Levy EB, Gomez-Jorge J. Uterine artery embolization for leiomyomata. Obstet Gynecol. 2001;98(1):29–34.
45. Walker WJ, Pelage JP. Uterine artery embolisation for symptomatic fibroids: clinical results in 400 women with imaging follow up. BJOG. 2002;109(11): 1262–72.
46. Pron G, Bennett J, Common A, Wall J, Asch M, Sniderman K, Ontario Uterine Fibroid Embolization Collaboration Group. The Ontario Uterine Fibroid Embolization Trial. Part 2. Uterine fibroid reduction and symptom relief after uterine artery embolization for fibroids. Fertil Steril. 2003;79(1):120–7.
47. Walker WJ, Barton-Smith P. Long-term follow up of uterine artery embolisation—an effective alternative in the treatment of fibroids. BJOG. 2006;113(4): 464–8.
48. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril. 2009;91(4):1215–23.
49. Homer H, Saridogan E. Uterine artery embolization for fibroids is associated with an increased risk of miscarriage. Fertil Steril. 2010;94(1):324–30.
50. Mara M, Fucikova Z, Maskova J, Kuzel D, Haakova L. Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine artery embolization and myomectomy. Cardiovasc Intervent Radiol. 2008;31:73–85.
51. Donnez J, Squifflet J, Polet R, Nisolle M. Laparoscopic myolysis. Hum Reprod Update. 2000;6(6):609–13.
52. Brucker SY, Hahn M, Kraemer D, et al. Laparoscopic radiofrequency volumetric thermal ablation of fibroids versus laparoscopic myomectomy. Int J Gynecol Obstet. 2014; (in press).
53. Garza Leal JG, Hernandez Leon I, Castillo Saenz L, Lee BB. Laparoscopic ultrasound-guided radiofrequency volumetric thermal ablation of symptomatic uterine leiomyomas: feasibility study using the Halt 2000 Ablation System. J Minim Invasive Gynecol. 2011;18(3):364–71.

54. Berman JM, Guido RS Garza Leal JG, Pemueller RR et al. Three-year outcome of the Halt trial: a prospective analysis of radiofrequency volumetric thermal ablation of myomas. J Minim Invasive Gynecol. 2014; (Epub ahead of print).
55. Kim CH, Kim SR, Lee HA, Kim SH, et al. Transvaginal ultrasound-guided radiofrequency myolysis for uterine myomas. Hum Reprod. 2011;26(3):559–63.
56. Garza-Leal J, Toub D, Hernandez León I. Transcervical, intrauterine ultrasound-guided radiofrequency ablation of uterine fibroids with the VizAblate System: safety, tolerability, and ablation results in a closed abdomen setting. Gynecol Surg. 2011;8(3):327–34.
57. Ren XL, Zhou XD, Zhang J, et al. Extracorporeal ablation of uterine fibroids with high-intensity focused ultrasound: imaging and histopathologic evaluation. J Ultrasound Med. 2007;26:201–12.
58. Ikink ME, Voogt MJ, Verkooijen HM, Lohle PN, Schweitzer KJ, Franx A, Mali WP, Bartels LW, van den Bosch MA. Mid-term clinical efficacy of a volumetric magnetic resonance-guided high-intensity focused ultrasound technique for treatment of symptomatic uterine fibroids. Eur Radiol. 2013;23(11): 3054–61.
59. Voogt MJ, Trillaud H, Kim YS, Mali WP, et al. Volumetric feedback ablation of uterine fibroids using magnetic resonance-guided high intensity focused ultrasound therapy. Eur Radiol. 2012;22(2):411–7.
60. Stewart EA, Rabinovici J, Tempany CM, Inbar Y, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. Fertil Steril. 2006;85(1):22–9.
61. Behera MA, Leong M, Johnson L, Brown H. Eligibility and accessibility of magnetic resonance guided focused ultrasound (MRgFUS) for the treatment of uterine leiomyomas. Fertil Steril. 2010;94:1864–8.
62. Arleo EK, Khilnani NM, Ng A, Min RJ. Features influencing patient selection for fibroid treatment with magnetic resonance-guided focused ultrasound. J Vasc Interv Radiol. 2007;18:681–5.
63. Kim HS, Baik JH, Pham LD, Jacobs MA. MR-guided high-intensity focused ultrasound treatment for symptomatic uterine leiomyomata: long-term outcomes. Acad Radiol. 2011;18(8):970–6.
64. Gorny KR, Woodrum DA, Brown DL, Henrichsen TL, et al. Magnetic resonance–guided focused ultrasound of uterine leiomyomas: review of a 12-month outcome of 130 clinical patients. J Vasc Interv Radiol. 2011;22:857–64.
65. Rabinovici J, David M, Fukunishi H, Morita Y, et al. Pregnancy outcome after magnetic resonance–guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. Fertil Steril. 2010; 93(1):199–209.
66. Maconochie N, Doyle P, Prior S, Simmons R. Risk factors for first trimester miscarriage; results from a UK-population-based case–control study. BJOG. 2007;114(2):170–86.
67. Zowall H, Cairns J, Brewer C, Lamping D, et al. Cost-effectiveness of magnetic resonance-guided focused ultrasound surgery for treatment of uterine fibroids. BJOG. 2008;115:653–62.
68. Kim Y, Bae DS, Park MJ, Viitala A, Keserci B, Rhim H, Lim HK. Techniques to expand patient selection for MRI-guided high-intensity focused ultrasound ablation of uterine fibroids. AJR Am J Roentgenol. 2014;202:443–51.

Laparoscopic Myomectomy

11

Radu Apostol, Mohamad Mahmoud, and Farr Nezhat

Laparoscopic myomectomy is an alternative to the abdominal approach, with fewer complications, shorter hospital stay, and less disability [1, 2]. The laparoscopic route for performing myomectomy has been proven feasible in numerous studies. With the advent of better insufflators, light sources, cameras, improvement in suturing instrumentation and techniques, as well as the availability of electronic morcellators, the rate of laparoscopic myomectomy has increased in the past decade after being limited by the technical and surgical skill challenges it presented.

Indications

There is no consensus on the exact criteria to determine the eligibility of a patient for laparoscopic myomectomy approach, as this depends on the skills of the surgeon performing the procedure. Indications for this procedure range from a single intramural or subserosal fibroid of 15 cm or less, or three or fewer fibroids of 5 cm or less in diameter each [3, 4], to uterine size ≤14 weeks after a 3-month course of GnRH agonist therapy with no individual myoma larger than 7 cm, to no myoma near the uterine artery or near the tubal ostia if fertility is desired and at least 50 % of the myoma be subserosal [5]. However, experienced surgeons have reported laparoscopic myomectomy on myomas of more than 10 cm [6] more than 15 cm [7], and even more than 20 cm in diameter [8]. Laparoscopic myomectomy of myomas exceeding 500 g in weight have also been reported [7, 9]. As a general rule, the ideal candidate, for laparoscopic myomectomy is a patient with fewer than three myomas, none larger than 8–9 cm or with pedunculated myomas regardless of the size.

R. Apostol, DO • M. Mahmoud, MD
Department of Obstetrics and Gynecology, St. Luke's and Roosevelt Hospitals, New York, NY, USA

F. Nezhat, MD, Prof, FACOG, FACS (✉)
Department of Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, USA

Division and Fellowship in Minimally Invasive Gynecologic Surgery and Robotics, Department of Obstetrics and Gynecology, Mount Sinai St. Luke's and Mount Sinai Roosevelt, USA

Department of Obstetrics, Gynecology and Reproductive Medicine, State University of New York at Stony Brook, School of Medicine, NY, USA

Minimally Invasive Gynecologic Surgery, Department of Obstetrics and Gynecology, Winthrop University Hospital, Mineola, NY, USA
e-mail: FNezhat@chpnet.org; fn0250@aol.com

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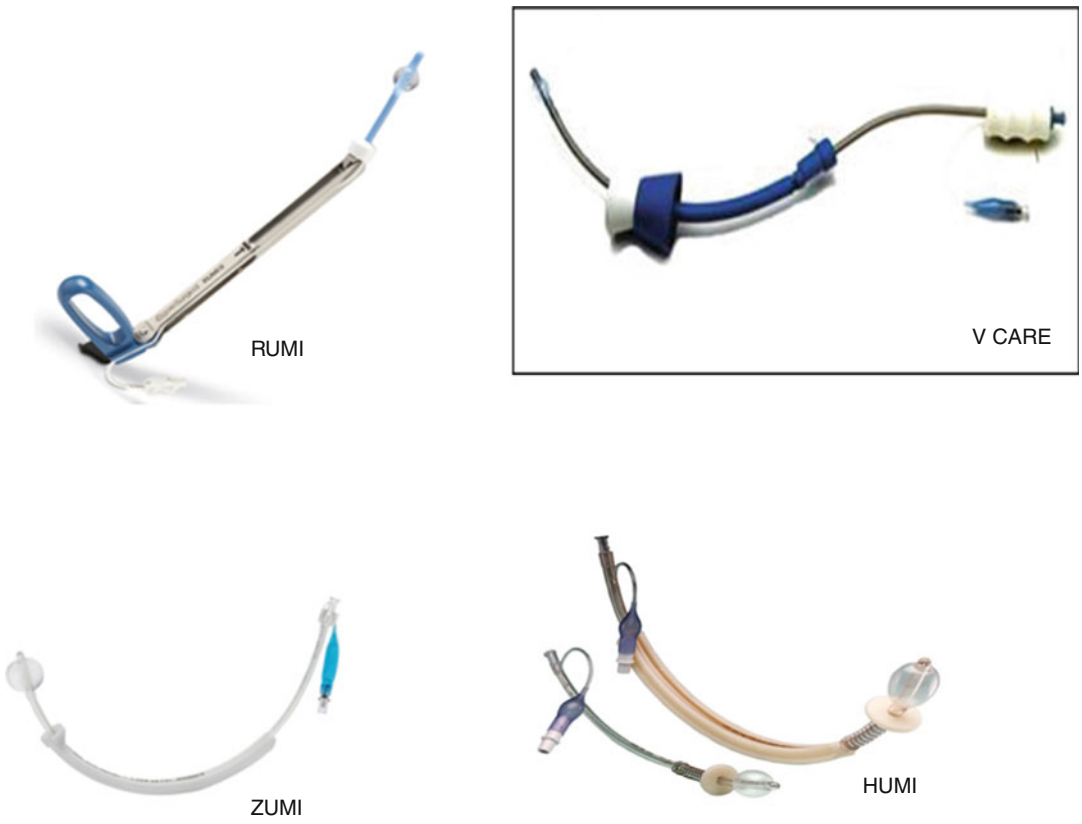

Fig. 11.1 Uterine manipulators (From Nezhat et al. [11]. © 2013 Cambridge University Press, reproduced with permission)

Technique

The patient is placed in the low lithotomy position using Allen stirrups (Allen Medical Systems, Cleveland, OH). Optimum safety in positioning is accomplished by tucking the arms at the patient's sides, with good padding around the elbows; placement on a gel pad or other device such as a beanbag or egg-crate foam to prevent sliding down the table, and using padded shoulder blocks if necessary. A variable amount of a dilute vasopressin solution (various dilutions have been used ranging from 20 Units (U) in 60 mL of saline, to 20 U in 100–400 mL of saline) is then injected transvaginally intracervically about 1–2 cm deep at both the 8 and 4 o'clock positions. This step can be bypassed by direct injection into the myometrium capsule. Cardiac arrest following injection of vasopressin of varying concentrations has been reported, but not typically when the total injected amount is less than 10–15 U [10], so it seems reasonable that if higher volume is desired, appropriate dilution is prudent. The half-life of vasopressin is 10–20 min, thus repeat administration should be used with caution because of the accumulation effect.

Laparoscopic myomectomy is facilitated by the use of a uterine manipulator. Different manipulators are suitable including those with a balloon such as Humi(Cooper surgical) or ZUMI(cooper surgical) (Fig. 11.1), or others. The balloon helps with the stabilization of the device within the uterus and also can identify the entrance into the endometrial cavity when the ballon is seen or ruptured.

The procedure is facilitated by the use of four ports, the sizes of which depend on the suturing technique employed by the surgeon, and the type of morcellation/extraction technique planned.

Generally, one can perform most laparoscopic myomectomies with a 5–10 mm umbilical port, and 1–2 ports, each 5 mm, on each side. One side port is typically at the level of the umbilicus or slightly caudad to it, while the other is medial to the anterior–superior iliac spine (ASIS). A lateral port may be placed above the umbilicus for larger uteri. A suprapubic 11–12-mm port may be placed to later facilitate morcellation.

Following exam under anesthesia, diagnostic hysteroscopy is a critical step in order to assess the uterine cavity for any pathology, such as intracavitary myoma or polyp or even synechias which need to be addressed in the same setting, especially if the myomectomy is performed for fertility reasons. Prior to the placement of the accessory ports, the size and position of the myomas are carefully assessed. If there is any doubt about safely performing the myomectomy via laparoscopy, a conventional or minilaparotomy should be performed. The threshold for conversion depends on the surgeon's skills and experience.

Pelvic cavity should be evaluated for any associated pathology, such as endometriosis, adhesions and tubo-ovarian pathology. Nezhat et al., reported that most patients with endometriosis have leiomyomas which we believe should be treated [12].

After proper placement of the trocars and complete survery of the pelvis and abdomen, dilute vasopressin solution is injected into the subserosa and myometrium overlying the myoma(s) until the tissue blanches. This is easily accomplished using a control-top syringe and a 4-in. 22-gauge spinal needle, which can be inserted percutaneously over the uterus, or using a laparoscopic needle tip device. The use of vasopressin for gynecologic surgery has been controversial, but is widely accepted in the US. In two prospective randomized studies, dilute vasopressin solution was found to decrease blood loss at time of myomectomy via laparotomy compared with placebo or a tourniquet [13]. An alternative to the use of vasopressin is to inject 0.25 % bupivacaine with epinephrine into the sub-serosa and myometrium in a similar fashion. This also has a vasoconstrictive effect and has been found in one randomized study to decrease the need for postoperative pain medication in women undergoing laparoscopic myomectomy as well as to decrease blood loss [14].

Another alternative, that requires advanced surgical skills, is the laparoscopic uterine artery occlusion prior to performing the enucleation of the myomas. This can be accomplished by either using a permanent or reversible clip, or energy coagulation of the uterine arteries at their origin from the hypogastric artery [15]. This technique has especially been found more helpful in challenging cases, such as the ones involving cervical myomas [16].

Pedunculated myomas are the least difficult to manage laparoscopically. Following the administration of dilute vasopressin into the stalk, the myoma is removed by cutting and coagulating the stalk. Care must be taken to stay close to the myoma and avoid thermal damage to the normal myometrium from which the stalk arises. An alternative, is to place one or two ties around the pedicle such as an Endoloop (Ethicon) and to excise the myoma with electrosurgery around its base approximately 1–2 cm above the insertion of the pedicle. The pedicle can then be over sewn to assure hemostasis. This technique minimizes the risk of later uterine rupture, which has been reported during pregnancy following laparoscopic removal of a pedunculated myoma [17, 18].

The removal of subserousal myomas is less challenging than the removal of deep intramural myomas. Dilute vasopressin is injected in multiple sites between the myometrium and the fibroid capsule. An incision is made on the serosa overlying the leiomyoma, using the CO_2 laser (superpulse or ultrapulse mode), a monopolar electrode (hook or scissors), a fiber laser, or harmonic scalpel or spatula. Traditionally, the incision has been oriented in the vertical direction, along the axis of the uterus. Some authors have found that incising transversely instead facilitates both the dissection and the repair. Once the incision is made, it is extended until it reaches the capsule. The myometrium retracts as the incision is made and the myoma bulges outward. Two grasping, toothed forceps can be used to hold the edges of the myometrium, and the suction–irrigator, or Kittner dissector or a Maryland dissector or the harmonic scalpel, can be used to shell the leiomyoma from its capsule. A myoma screw is inserted into the tumor or a single tooth tenaculum can be used

to grasp the myoma and to apply traction during blunt dissection. An alternative is to insert a finger through a 12-mm suprapubic port site incision and manually dissect the myoma free from the myometrium. Visible vessels are electrocoagulated before being cut. Following complete removal of the myoma(s), the uterine defect is irrigated. Bleeding points are identified and controlled, preferably with bipolar electrosurgery. Point coagulation of identifiable vessels can be accomplished by using short bursts of cutting or coagulation monopolar or bipolar current, however we highly advise against this, since excessive use of electrosurgery not only makes the repair of the myometrium more difficult but it also impedes tissue healing with subsequent risk of utero-peritoneal fistula and rupture during subsequent pregnancies. Instead, hemostatic agents such as Floseal (Baxter, Deerfield, IL) or Surgiflo (Ethicon Inc) can be used to decrease bleeding. The edges of the uterine defect are approximated by superficial suturing. Figures 11.2, 11.3, 11.4, 11.5 and 11.6 depict key steps of laparoscopic myomectomy.

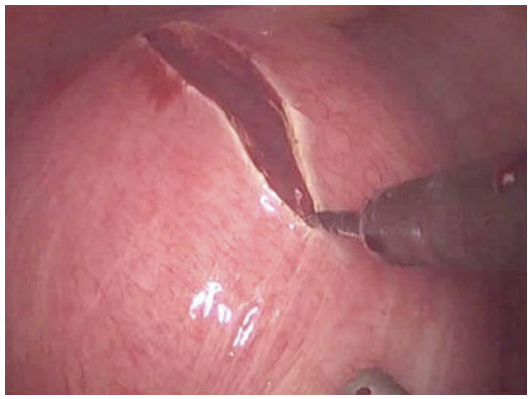

Fig. 11.2 Uterine incision

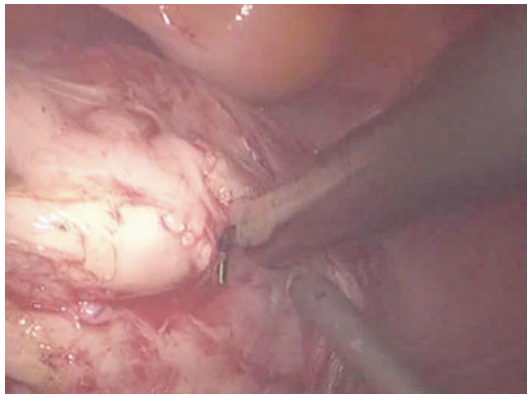

Fig. 11.3 Dissection of the myoma

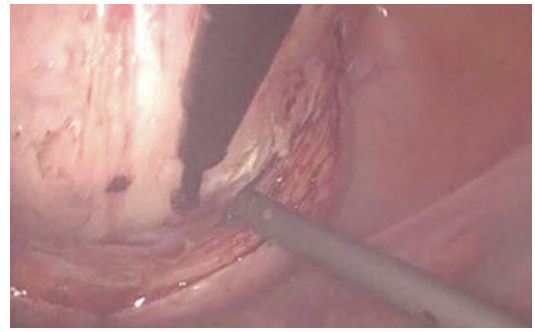

Fig. 11.4 Enucleation of the myoma

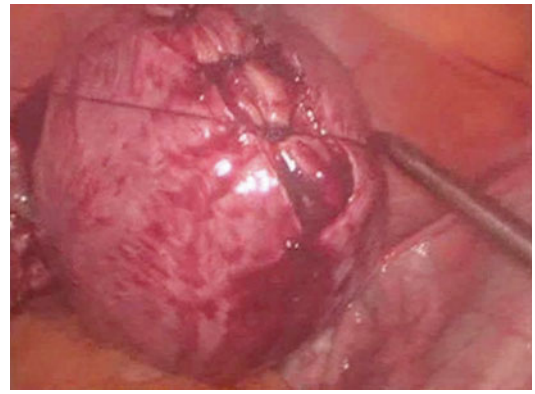

Fig. 11.5 Closure of the myometrial defect

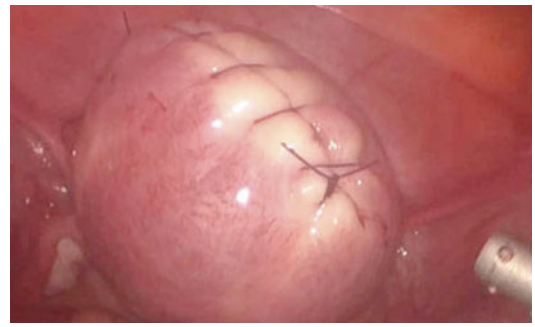

Fig. 11.6 Hemostatic closed incision

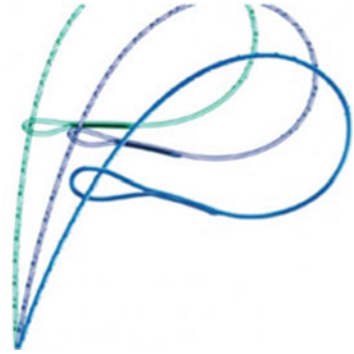

Fig. 11.7 Barbed suture (From Nezhat et al. [11]. © 2013 Cambridge University Press, reproduced with permission)

Deep intramural or broad ligament intramural myomas are the most difficult to properly manage laparoscopically and should be done only by surgeons skilled in laparoscopic suturing. This is especially true if the patient plans future childbearing. The myometrial closure traditionally recommended following open myomectomy is a three-layered closure beginning at the base of the defect, to obliterate the dead space, with figure of- eight or horizontal mattress sutures. A second layer of continuous suture is then placed to further approximate the myometrium and finally ending with a continuous imbricating "baseball" stitch on the serosa. Synthetic absorbable polyglactin sutures (Vicryl, Ethicon, Somerville, NJ; Polysorb, USSC, Norwalk, CT) are recommended because they produce less inflammatory reaction than catgut. True comparisons of alternative suturing methods have not been performed. Intraligamentous and broad ligament myomas require careful identification of the course of the ureters, the bladder, and pelvic sidewall blood vessels. Depending on the location of the myoma, an incision is made on the anterior or posterior leaf of the broad ligament. The myoma is removed with the techniques described above for subserosal and intramural tumors. Throughout the procedure, the location of the ureters is noted. Hemostasis is obtained with sutures, clips, or bipolar forceps. The broad ligament and peritoneum are not closed but allowed to heal spontaneously. Drains are used infrequently.

Stringer and associates [19] described a simplified way of closing deep myometrial defects using the Endo Stitch automatic suturing device (United States Surgical, Norwalk CT) [17]. Multiple layers of continuous interlocking sutures are placed using this device, which captures the 9-mm needle in the opposite jaw when the handles are squeezed. The suture is held taut by the assistant, and finally an intracorporeal knot is tied with the device. The Endo Stitch must be used through a 10-mm port. Its limitations are a semi-straight needle that is relatively short, making it a challenge to grasp adequate amounts of uterine tissue in each bite. Some surgeons feel this can be faster than conventional open suturing techniques.

The introduction of the Quill™ bidirectional barbed suture (Angiotech Pharmaceuticals, Inc., Vancouver, BC, Canada) and later the "V-LOC" (Covidien, Mansfield, M) (Fig. 11.7) have changed the way laparoscopic myomectomies are performed. The barbs minimize tissue recoil and do so with accurate soft tissue approximation, achieving hemostasis without the use of locking and figure eight sutures. Barbed suture allows for a shorter operative time, as there is an ease of suturing without the complication of knot tying. The advantages of using barbed sutures in this setting include the ability to perform knotless suturing and rapid suture deployment, which may result in decreased operative time and blood loss. In addition, the tensile strength of the suture is maintained by the barbs, which facilitates the operative procedure and may potentially lead to a more even distribution of tension along the closure [15, 20–22]. If these types of suture were to be used on the serosa of the uterus, one should take care not to leave extra suture behind, since this raises the risk of post-operative bowel obstruction.

Specimen Removal Techniques

Other than laparoscopic suturing, the greatest challenge and often the most frustrating step in laparoscopic myomectomy is specimen removal. For multiple small myomas, the enucleated specimens can be placed in a specimen retrieval bag, brought up to the largest port site, morcellated in

the bag at the skin line using an 11 scalpel blade or scissors. While the introduction of power morcellators, in the last decade, has revolutionized the laparoscopic myomectomy procedure, due to its ease of use, there have recently been serious concerns regarding the safety of its use. The most widely used devices in the US are made by Gynecare (Johnson & Johnson, Somerville, NJ), Karl Storz, WISAP, and Richard Wolf. Seeding of port sites with malignant cells or endometriosis is a well-known sequela of laparoscopic procedures. This may also occur with morcellated myoma tissue, as was shown in a case report by Ostrzenski [23]. Intra-abdominal seeding of benign leiomyoma could lead to parasitic leiomyomas that can become symptomatic or require further surgery [24, 25]. However, more concerning is the morcellation of an unsuspected leiomyosarcoma, that can lead to seeding of malignant tissue in the abdominal cavity, significantly altering the stage and prognosis of the disease [26]. Since there is no reliable test that could predict the presence of leiomyosarcoma in a leiomyomatous uterus, and based on recent reported cases of disseminated leiomyosarcoma following power morcellation [27], the US Food and Drug Administration (FDA) had issued a warning that discourages the use of laparoscopic power morcellation during hysterectomy or myomectomy for uterine fibroids, as of April 2014 (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm393576.htm). This has followed same warning issued by multiple societies including the Society of Gynecologic Oncologists (SGO), the American Association of Gynecologic Laparoscopists (AAGL) and American College of Obstetrics and Gynecology (ACOG). As a result, multiple hospital systems throughout the United States have banned the use of power morcellators. However, there are multiple alternatives available to power morcellation. One alternative includes the removal of the specimen through a posterior and occasionally anterior colpotomy incision. The posterior colpotomy incision can be done vaginally below the cervix between the uterosacral ligaments. Once the peritoneum is opened, the myoma is grasped vaginally in a bag with a tenaculum or Leahy clamp and removed intact or progressively morcellated using a coring technique, while enclosed in a laparoscopic bag. Alternatively, the vagina can be identified laparoscopically with the help of the uterine manipulator, vaginal probe, or a sponge stick placed in the posterior fornix. An incision is then made laparoscopically using an electrosurgical needle, scissors, harmonic scalpel, or CO_2 laser. The disadvantage of this approach is that the pneumoperitoneum is rapidly lost, making it difficult to bring the myoma into the cul-de-sac. A wet lap pad or a surgical glove containing 2 wet sponges (also known as Ceana's glove), may be placed in the vagina to restore the pneumoperitoneum and view the pelvis. Recently, the development of automatic insufflators, such as the AirSeal system (SurgiQuest, Connecticut), that re-fills the pneumoperitoneum when the vagina is open or gas leaks are present, make the procedure easier. Multiple small myomas can be removed with a specimen retrieval bag placed through the colpotomy incision. The colpotomy incision can be sutured laparoscopically or vaginally.

Another alternative method that we prefer is the use of laparoscopically assisted myomectomy/minilap myomectomy (LAM). This technique was first reported by Nezhat et al. in 1994 [28] and is less difficult and requires less time to complete than other modes of myomectomy. The decision to perform a LAM is usually made intraoperatively following completion of exploratory laparoscopy and treatment of other pelvic abnormalities. Cases most suitable for a LAM include a myoma greater than 8 cm, multiple myomas requiring extensive morcellation, a deep, large, intramural myoma that requires uterine repair in multiple layers. A combination of laparoscopy and a 2–4 cm abdominal incision may put laparoscopic myomectomy within the technical reach of more gynecologists. Better pelvic exposure during the laparoscopy allows the gynecologist to diagnose and treat associated endometriosis or adhesions, and the traditional access allows for fast morcellation and conventional suturing preserving myometrial integrity. In addition, LAM with morcellation and conventional suturing may reduce the mean operative time. Similar benefits may be seen with the introduction of barbed suture. Further support for the LAM technique is

Fig. 11.8 Self-retaining wound retractor (From Nezhat et al. [11]. © 2013 Cambridge University Press, reproduced with permission)

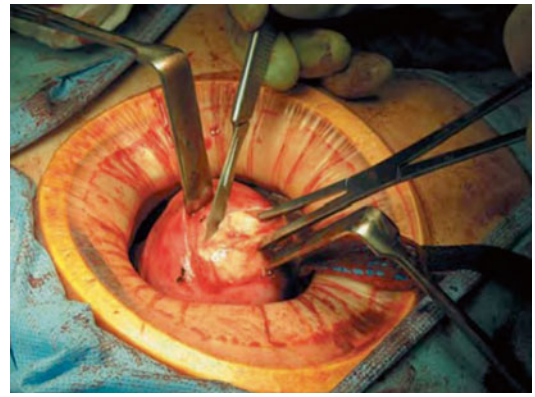

Fig. 11.9 Laparoscopic assisted myomectomy

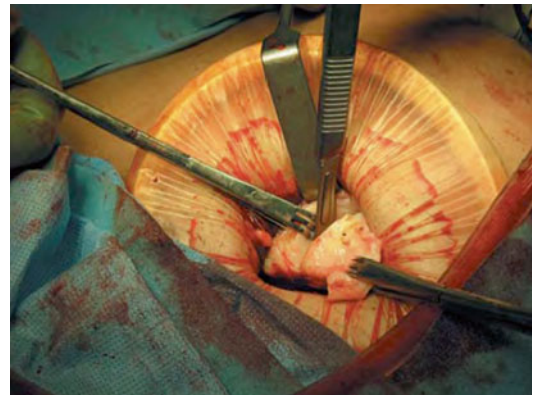

Fig. 11.10 Laparoscopic assisted myomectomy (Shelling and morcellation of leiomyoma)

found in a study of in a study by Glasser that detailed 139 minilaparotomy myomectomies [29]. Out of the 139 cases presented, 66 underwent LAM, during which the laparoscope was used to identify and mark the incision site or to perform adhesiolysis. The authors concluded that myomectomy performed through a 3–6 cm minilaparotomy incision affords the advantage of same-day discharge as well as the ability to palpate the uterus and close the defect using a standard three-layered suturing technique. The most prominent myoma is injected at its base with 3–7 mL of diluted vasopressin. An incision is made over the uterine serosa at the surface of the tumor and extended until the capsule of the leiomyoma is reached. A corkscrew manipulator is inserted into the leiomyoma and used to elevate the uterus toward the midline suprapubic puncture. Alternatively a laparoscopic single tooth tenaculum can be used for the same purpose. With the trocar and manipulator attached to the myoma, a 4–6 cm transverse incision is made through skin and fascia and the rectus muscle separated in the midline. After opening the peritoneum transversely, an Alexis wound retractor (Applied medical) or a Mobius abdominal retractor (Cooper surgical) (Fig. 11.8) is introduced for better exposure. The leiomyoma is grasped with two Lahey tenacula (Fig. 11.9). The tumor is shelled and morcellated sequentially (Fig. 11.10), and after its complete removal, the uterine wall defect shows through the incision. When multiple leiomyomas are found, as many as possible are removed through one uterine incision if it can be accomplished without excessive tunneling. When other myomas are located and cannot be removed through the initial uterine incision, the 4-cm abdominal opening is approximated temporarily with two or three Allis clamps, or an inflated latex glove (placed over the self-retaining retractor while the insufflator is turned ON). The laparoscope is reintroduced, and the remaining myomas are identified, and brought to the incision and removed in a similar fashion. The uterus is then repaired in two to three layers (Fig. 11.11). The abdominal incision is then closed in routine fashion, ideally with a subcuticular skin closure. The laparoscope is used to evaluate hemostasis. The pelvis is observed to detect and treat endometriosis and adhesions that may have been obscured previously by myomas. Copious irrigation is used, blood clots are removed, and

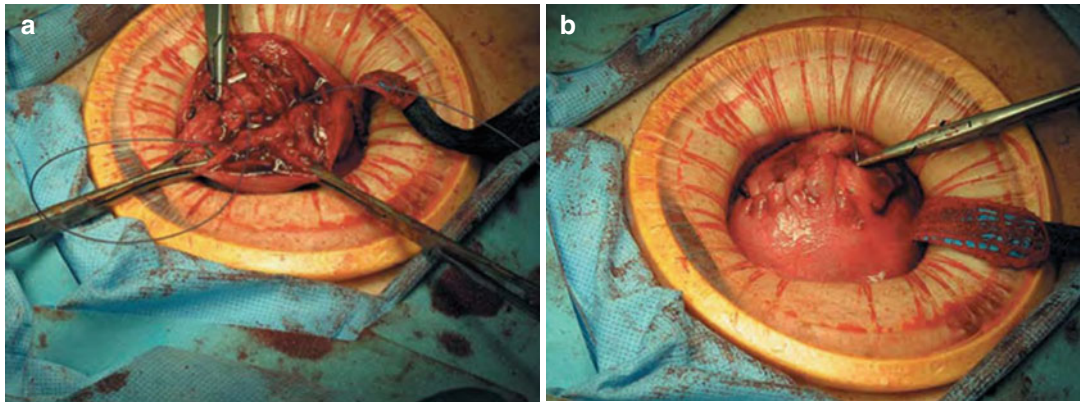

Fig. 11.11 (**a**, **b**) Laparoscopic assisted myomectomy (Closure of myometrium)

Interceed (Gynecare, Somerville, NJ) may be applied over the uterus to help prevent adhesions if the incision is completely dry. Nezhat and associates evaluated 143 charts from their practice [30], including those of patients who had myomectomy by laparotomy (15.3 %), laparoscopic myomectomy (44.7 %), or LAM (39.8 %). Mean operating times, estimated blood loss, hospital stay (after eliminating the first 15 LAM patients), and time to resume work or regular activities were the same for laparoscopic myomectomy and LAM despite larger myomas, difficult locations of intramural myomas, and adjunctive laparoscopy in the latter group. The leiomyoma weights were greater in the LAM group than in the laparoscopic myomectomy group ($P \leq 0.05$). Time to 100 % recovery was slightly longer in the LAM group. Most patients are observed in an outpatient unit and discharged the morning after the operation, although some can leave the hospital on the afternoon or evening of the procedure.

Role of GNRH Prior to Laparoscopic Myomectomy

Pre-treatment with GnRH agonists before myomectomy remains controversial. In a systematic review of randomized controlled trials of the use of GnRH analogues before hysterectomy and myomectomy, it was found that pre- and postoperative blood counts were improved, uterine and myoma volume decreased, and operative time and blood loss reduced by GnRH agonist therapy [31]. Reduction in leiomyoma size makes the procedure less time-consuming because a smaller uterine incision can be made and less morcellation is required. The individual myomas, however, are softer, which often results in the clamps tearing through the tissue, resulting in the loss of upward traction, which is counterproductive and may result in increased bleeding. Thus, although GnRH agonist treatment may soften the myoma (facilitating morcellation) and shorten operative times, it also may increase the duration of laparoscopic or minilaparotomy myomectomy [32]. For anemic patients, preoperative GnRH treatment may enable restoration of a normal hematocrit, decrease the size of the myoma, and reduce the need for transfusion [33]. However, not all studies have shown the benefits described above. Increased difficulty in identifying and dissecting the cleavage planes and shrinking small myomas to the point at which they cannot be seen or palpated may increase recurrence [34]. In a recent meta-analysis by Chen et al. looking at the effect of preoperative GnRH use prior to laparoscopic myomectomy, GnRH agonist did not reduce operative time [35]. However, intraoperative blood loss was statistically lowered (mean difference, 60 mL; 95 % confidence interval [CI], 39–82). Statistical difference was also observed in postoperative hemoglobin concentration (mean difference, 1.15 g/dL; [95 % CI, 0.46–1.83]) and red blood cell count (mean difference,

0.65 × 10(6) cells/mL; [95 % CI, 0.16–1.14]) but not serum iron concentration. In our practice, we do not use routinely preoperative GnRH agonists, unless the patient is anemic.

Adhesion Prevention

Post-myomectomy adhesions have long been thought to possibly compromise fertility, although sound data is lacking. Single, vertical, anterior and midline uterine incisions may cause fewer adhesions. Although sutures predispose patients to adhesions [36] they are necessary to close the uterine defect. Both Seprafilm [37] (HAL-F) bioresorbable membrane (Genzyme Corporation, Cambridge, MA) and Interceed (oxidized regenerated cellulose) [38], have been shown to reduce postoperative adhesions in this setting. However, the impact on fertility was not assessed in these studies, and their routine use cannot be advocated for this purpose [39, 40]. Regardless of the adhesion prevention material used, most are ineffective in the absence of hemostasis. This was shown very early in a study on animal models by Linsky and associates [41]. Using an imbricating baseball-type closure on the uterine serosa is both hemostatic and minimizes the presence of raw edges, which could possibly predispose to adhesion formation.

Uterine Rupture Following Laparoscopic Myomectomy

Spontaneous uterine rupture of the gravid uterus following laparoscopic myomectomy has been reported in all types of leiomyomas including pedunculated, subserosal or intramural types, mainly in the 2nd and 3rd trimesters of pregnancy [42, 43]. In a review of 19 case reports of uterine rupture following laparoscopic myomectomy, published between 1992 and 2004 [42], looking at risk factors for uterine rupture, the authors concluded that in order to decrease the risk of this complication surgeons need to adhere to techniques developed for abdominal myomectomy including limited use of electrosurgery and multilayered closure of the myometrium. The necessity for complete closure of the defect cannot be emphasized enough. It is inadequate to place two or three large through-and through interrupted sutures in a deep myometrial defect if the patient plans future childbearing. Other reports of uterine rupture following laparoscopic myomectomy emphasize the importance of adequate closure of the myometrial defect [44–46]. A recent study reported the appearance of myomectomy scars in 15 women undergoing elective cesarean delivery because of previous myomectomy [47]. The scars in the five women who had myomectomies performed laparoscopically were all described as "strained with thinned tissue and illdefined edges" despite being sutured. In the 10 women who had their myomectomy performed by laparotomy, the majority of scars were symmetric, with the tissue being of uniform thickness compared with the surrounding myometrium. Certainly the liberal use of electrocautery for hemostasis might be the etiologic factor in uterine rupture. In summary, patients must be thoroughly counseled about the possibility of uterine rupture at any time during the gestation, and made aware of the possibility of fetal loss and even hysterectomy, if hemorrhage cannot be controlled. During pregnancy, these patients should be followed carefully and all complaints of abdominal pain addressed immediately. Despite the lack of evidence, the most common practice among obstetricians is to recommend cesarean delivery in future pregnancies for patients with a history of myomectomy regardless of the approach, especially if the uterine cavity has been penetrated during the myomectomy [48]. In our practice, we recommend cesarean delivery when there is deep myometrial invasion, regardless whether or not the uterine cavity was entered.

At second-look laparoscopy, we have observed indentations at the sites from which leiomyomas were removed that were directly proportioned to the size of the myomas removed and may therefore represent structural defects [49]. In patients with intramural fibroids and significant uterine wall defects, an unacceptably high rate of endometrial-serosal fistula occurs. Uteroperitoneal fistulas also have been noted after laparoscopic myomectomy [30].

Pregnancy Following Myomectomy

Pregnancy rates after myomectomy, both by laparotomy and laparoscopic, have been variable. Several studies comparing reproductive outcomes after laparoscopic or abdominal myomectomy showed no significant difference between the two approaches [50–53].

Chu Jin et al., performed a meta-analysis looking at randomized trials comparing laparoscopic and open myomectomy for patients with leiomyomas in regards to operative parameters and outcomes. Six studies and 576 patients were studied. Their data analysis showed that laparoscopic myomectomy was associated with less hemoglobin drop, reduced operative blood loss, more patients fully recuperated at day 15, diminished postoperative pain, and fewer overall complications but longer operation time. However, major complications, pregnancy and recurrence were comparable in the two groups [54].

There are many factors that determine the reproductive outcome following myomectomy, including the age of the patient and the number, size, and location of the myomas [55]. In a retrospective study of 67 women who had undergone myomectomy, the majority of which were done by laparotomy, Sudik et al. reported higher pregnancy rates in women with fewer than six myomas removed [56]. Although myoma location did not influence the results in this study, women with a larger myoma volume (≥100 ml) removed had higher pregnancy rates. In a retrospective review of 103 women who had undergone laparoscopic myomectomy in France, Desolle and associates found a significantly higher pregnancy rate in women with unexplained infertility [57], those younger than 35 years of age, and those with less than 3 years of infertility. Neither the number of myomas removed nor their location or size had any significant influence on pregnancy rates. The authors concluded other factors involved in the patients' infertility were probably more important than the characteristics of the myomas. In a 5-year review of the anticipated benefits of myomectomy, Olufowobi and associates in the UK found that the symptomatic benefit was less (36 %) in the "infertility group" [58]. Following an observation period of 12–36 months, 17 patients in the infertility group were lost to follow-up. Two of the 14 patients (14 %) who attempted in-vitro fertilization (IVF) were successful. In the non-IVF group, 13 of the 28 (46 %) achieved natural conception. These results suggested that symptomatic improvement and fertility enhancement may be possible in some patients with fibroids. The authors felt that in view of the risks and potential failure of treatment associated with myomectomy, their results, yet again, support the fact that patients should be properly counseled before embarking on myomectomy.

In a retrospective analysis of 72 women with intramural and subserosal myomas, Marchionni and associates in Italy found the conception rate was 28 % before myomectomy and 70 % after surgery [59]. The corresponding figures were 69 and 25 % for pregnancy loss and 30 and 75 % for live birth rate, respectively. Age 30 years or younger and number of fibroids removed were the only significant and independent predictors of obstetric outcome by multivariate analysis. Their results suggested that abdominal myomectomy might improve reproductive outcome in patients with intramural and subserosal fibroids. The reproductive performance was particularly good when the patients were younger than 30 years and had a single myoma to remove. In a prospective randomized study of 131 women comparing myomectomy by laparoscopy versus laparotomy, Seracchioli and associates found pregnancy rates were no different (55.9 % in the laparotomy group VS. 53.6 % in the laparoscopy group) [60]. In another retrospective study by the same investigator, 514 patients of fertile age underwent LM. A total of 158 pregnancies were achieved. There were 43 (27.2 %) spontaneous abortions, 4 (2.6 %) ectopic pregnancies, and 1 (0.6 %) therapeutic abortion. Only 27 patients (25.5 %) had vaginal deliveries, whereas 79 (74.5 %) underwent cesarean section. No instances of uterine rupture were recorded [61].

In a retrospective study comparing reproductive outcomes after uterine artery embolization for fibroids versus laparoscopic myomectomy, Goldberg and associates found that pregnancies after uterine artery embolization had higher rates of preterm delivery (odds ratio, 6.2; 95 % CI,

1.4–27.7) and malpresentation (odds ratio, 4.3; 95 % CI, 1.0–20.5) than did pregnancies after laparoscopic myomectomy. The risks of postpartum hemorrhage (odds ratio, 6.3; 95 % CI, 0.6–71.8) and spontaneous abortion (odds ratio, 1.7; 95 % CI, 0.8–3.9) after uterine artery embolization were similarly higher than the risks after laparoscopic myomectomy; however, these differences were not statistically significant. They concluded that pregnancies in women with fibroids who were treated by UAE, compared with pregnancies after laparoscopic myomectomy, were at increased risk for pre-term delivery and malpresentation. The wide confidence intervals for the results indicate that the study had limited statistical power [62].

Surrey and associates evaluated the impact of myomectomy on IVF–embryo transfer (IVF-ET) and oocyte donation cycle outcome [63]. The study was carried out within one center and involved treatment of myomas that distorted the uterine cavity only, whether submucosal or intramural. A total of 101 patients underwent surgical treatment for leiomyomas: 46 submucosal with hysteroscopic resection and 55 intramural treated with open laparotomy. Patients who underwent surgical myomectomy for what was felt to be clinically significant leiomyomas had assisted-reproductive technology cycle outcomes similar to those of a control population with regard to implantation, ongoing pregnancy, and early pregnancy loss. Neither the size nor the surgical approach altered the outcome. Pregnancy rates in the donor oocyte group were higher in patients who underwent surgical myomectomy as opposed to the control group, with no increase in biochemical pregnancies. Uterine cavity distortion, rather than size, was the criteria employed in this study. The study also mandated a diagnostic hysteroscopy in all patients to rule out any cavity distortions or endometrial lesions, including postoperatively. The authors stress the lack of strong correlation between either hysterosalpingography or traditional standard transvaginal sonography and hysteroscopic findings. As it would be expected, the mean number and size of leiomyomas were significantly larger in patients who underwent abdominal myomectomy. However, neither ongoing pregnancy nor implantation rates were significantly different in comparison with controls among either oocyte donor recipients (group A – hysteroscopic resection: 86.7 %, 57.8 %; group B – myomectomy: 84.6 %, 55.2 %; group C – no surgery: 77 %, 49.1 %). The findings were similar for those undergoing IVF-ET in comparison with controls (group 1: 61 %, 24 %; group 2: 52 %, 26 %; group 3: 53 %, 23 %).

Oliveira and associates in Brazil looked at the effects of intramural and subserosal uterine fibroids on the outcome of IVF-ET when there is no compression of the endometrial cavity [64]. In a retrospective, matched-control study from January 2000 to October 2001 done in a private IVF center, 245 women with subserosal and/or intramural fibroids that did not compress the uterine cavity (fibroid group) and 245 women with no evidence of fibroids anywhere in the uterus (control group) were studied. The type of fibroid (intramural, subserosal) and the number, size (centimeters), and location of intramural leiomyomas (fundal, corpus) were recorded and outcomes of IVF– intracytoplasmic sperm injection (ICSI) cycles were compared between the two groups. There was no correlation between location and number of uterine fibroids and the outcomes of IVF-ICSI. Patients with subserosal or intramural fibroids 4 cm or smaller had IVF-ICSI outcomes (pregnancy, implantation, and abortion rates) similar to those of controls. Patients with intramural fibroids 4 cm or greater had lower pregnancy rates than did patients with intramural fibroids 4 cm or less. There were no statistical differences related to delivery rates (31.5 % vs. 32 %, respectively) between all patients with fibroids and controls. The authors concluded that patients having subserosal or intramural leiomyomas 4 cm or smaller not encroaching on the uterine cavity have IVF-ICSI outcomes comparable to those of patients without such leiomyomas. Therefore, these patients might not require myomectomy before being scheduled for assisted reproduction cycles. However, the investigators recommend caution for patients with fibroids 4 cm or larger, and that such patients be treated before they are enrolled in IVF-ICSI cycles.

In a retrospective analysis of 106 infertile women with uterine leiomyomas, of whom 88

women underwent laparoscopic myomectomy and 18 laparoconversion, Soriano et al. found no difference in the pregnancy rate between the laparoscopic and laparoconversion groups (48 and 56 %, respectively). The mean time before conception in the laparoscopic and laparoconversion groups was 7.5 ± 2.6 and 15.1 ± 2.4 months, respectively ($P < 0.001$). There was no difference between the two groups in regards to the rates of pregnancy-related complications and vaginal delivery, and no uterine rupture occurred. They concluded that laparoscopic myomectomy is feasible and safe, and should be considered for infertile women with uterine fibroids. Fertility and pregnancy outcomes following laparoscopic myomectomy are comparable with those following myomectomy after laparoconversion [53].

In another recent retrospective study by Bernardi et al., 59 women age 23–42 years with the desire to have children and who underwent LM for symptomatic uterine leiomyoma were followed for a period of 73.55 months. The post-LM conception rate was 68 %. The proportion

of miscarriages ($n = 16$) among all pregnancies ($n = 55$) was lower after (24 %) than before (43 %) LM. Thirty-nine (46 %) deliveries were primary cesarean sections (CS). CS was performed due to patients' preference, placental complications, and uterine rupture (UR). Labor was successful in 62 % of all vaginal delivery trials. UR and placental complications occurred in 10 and 13 % of all pregnancies, respectively. They concluded that LM reduced the abortion rate and increased the CS rate in the cohort. UR risk may have been affected by suturing technique, the size and location of myomas removed [65].

In summary, there is no consensus on the impact of myomectomy on pregnancy rates, whether laparoscopic or by laparotomy. Preemptive myomectomy in the asymptomatic patient who desires fertility remains one of the most controversial subjects in gynecology. One must remember that myomectomy carries the risk of emergency hysterectomy in about 1 % of cases [66]. Also, postoperative infection and adhesion formation might in itself cause infertility. It seems that pregnancy has little or no effect on the overall size of fibroids despite the occurrence of red degeneration in early pregnancy. Fibroids, however affect pregnancy and delivery in several ways, with abdominal pain, mid-trimester loss, malpresentation, and difficult delivery being the most frequent complications. The size, location, and number of fibroids and their relation to the placenta are critical factors [67]. It seems apparent that a 4-cm intracavitary myoma will certainly interfere with the ability to maintain a pregnancy. Most gynecologic surgeons will perform myomectomy for intramural fibroids that are clearly symptomatic or are 6 cm or greater in diameter.

Recurrence of Leiomyomas

In a retrospective review of 114 women the recurrence of myomas was found to be higher after laparoscopic surgery than by laparotomy. (Nezhat FR 1998) However, in a systematic review of six randomized trials comparing laparoscopic with open myomectomy in 576 women, there was no significant difference in the rate of recurrent myomas between the two surgical approaches [54].

In a retrospective study of 512 women who underwent laparoscopic myomectomy it was found that the cumulative probability of leiomyoma recurrence increased steadily during the follow-up period, 11.7 % after 1 year, 36.1 % after 3 years, 52.9 % at 5 years, and reached 84.4 % at 8 years [68]. Furthermore, the rates of re-operation for recurrent leiomyoma was much lower: 6.7 % at 5 years and 16 % at 8 years. Significant risk factors that were independently associated with cumulative recurrence were: age, preoperative number of myoma, preoperative uterine size by pelvic examination, presence of associated pelvic disease, and delivery after laparoscopic myomectomy. It was concluded that the risk of recurrence of leiomyoma after laparoscopic myomectomy is linked with the age, preoperative number of leiomyoma, preoperative uterine size, presence of associated pelvic disease, and childbirth after surgery.

Undoubtedly, laparoscopic myomectomy offers superior outcomes when compared to traditional laparotomy, however it is clear that even in highly

trained clinicians, patients must be well selected for the procedure based upon the size, number and location of the myomas. It is most important that gynecologists employ only the minimally invasive techniques they are skilled in performing, and not be afraid to convert to laparotomy if they encounter difficulties.

References

1. Nezhat C, Nezhat F, Silfen SL, Schaeffer N, Evans D. Laparoscopic myomectomy. Int J Fertil. 1991; 36(5): 275–80.
2. Dubuisson JB, Lecuru F, Foulot H, Mandelbrot L, Aubriot FX, Mouly M. Myomectomy by laparoscopy: a preliminary report of 43 cases. Fertil Steril. 1991;56: 827–30.
3. Agdi M, Tulandi T. Minimally invasive approach for myomectomy. Semin Reprod Med. 2010;28: 228–34.
4. Kuwatsuru R. The indications, surgical techniques, and limitations of laparoscopic myomectomy. JSLS. 2003;7:89–95.
5. Parker WH, Rodie IA. Patient selection for laparoscopic myomectomy. J Am Assoc Gynecol Laparosc. 1994;2:23–6.
6. Paul PG, Koshy A, Thomas T. Laparoscopic myomectomy: feasibility and safety – a retrospective study of 762 cases. Gynecol Surg. 2006;3:97–102.
7. Yoon HJ, Kyung MS, Jung US, Choi JS. Laparoscopic myomectomy for large myomas. J Korean Med Sci. 2007;22:706–12.
8. Madhuri TK, Kamran W, Walker W, Butler-Manuel S. Synchronous uterine artery embolization and laparoscopic myomectomy for massive uterine leiomyomas. JSLS. 2010;14:120–2.
9. Walid MS, Heaton RL. Laparoscopic myomectomy: an intent-to-treat study. Arch Gynecol Obstet. 2010; 281:645–9.
10. Frishman G. Vasoressin: if some is good, is more better? Obstet Gynecol. 2009;113:476–7.
11. Nezhat C, Nezhat F, Nezhat C, editors. Video-assisted and robotic-assisted laparoscopy and hysteroscopy with DVD. 4th ed. Cambridge, UK/New York: Cambridge University Press; 2013.
12. Huang JQ, Lathi RB, Lemyre M, Rodriguez HE, Nezhat CH, Nezhat C. Coexistence of endometriosis in women with symptomatic leiomyomas. Fertil Steril. 2010;94:720–3.
13. Fletcher H, Frederick J, Hardie M, et al. A randomized comparison of vasopressin and tourniquet ashemostatic agents during myomectomy. Obstet Gynecol. 1996;87:1014–8.
14. Zullo F, Palomba S, Corea D, et al. Bupivacaine plus epinephrine forlaparoscopic myomectomy: a randomized placebo-controlled trial. Obstet Gynecol. 2004;104:243–9.
15. Alessandri F, Remorgida V, Venturini PL, Ferrero S. Unidirectional barbed suture versus continuous suture with intracorporeal knotsin laparoscopic myomectomy: a randomized study. J Minim Invasive Gynecol. 2010;17(6):725–9.
16. Matsuoka S, Kikuchi I, Kitade M, Kumakiri J, Kuroda K, Tokita S, Kuroda M, Takeda S. Strategy for laparoscopic cervical myomectomy. J Minim Invasive Gynecol. 2010;17:301–5.
17. Lieng M, Istre O. Uterine rupture after laparoscopic myomectomy. J Am Assoc Gynecol Laparosc. 2004;11(1):92–3.
18. Torbé A, Mikołajek-Bedner W, Kałużyński W, Gutowska-Czajka D, Kwiatkowski S, Błogowski W, Rzepka R, Czajka R. Uterine rupture in the second trimester of pregnancy as an iatrogenic complication of laparoscopic myomectomy. Medicina (Kaunas). 2012;48:182–5.
19. Stringer NH, McMillan NA, Jones RI, et al. Uterine closure with the endo stitch 10-mm laparoscopic suturing device – a review of 50 laparoscopic myomectomies. Int J Fertil Womens Med. 1997;42:288–96.
20. Greenberg JA, Einarsson JI. The use of bidirectional barbed suture in laparoscopic myomectomy and total laparoscopic hysterectomy. J Minim Invasive Gynecol. 2008;15(5):621–3.
21. Manoucheri E, Einarsson JI. The use of barbed suture in hysterectomy and myomectomy. Surg Technol Int. 2013;23:133–6.
22. Soto E, Flyckt R, Falcone T. Minimally invasive myomectomy using unidirectional knotless barbed suture. J Minim Invasive Gynecol. 2014;21(1):27.
23. Ostrzenski A. Uterine leiomyoma particle growing in an abdominal-wall incision after laparoscopic retrieval. Obstet Gynecol. 1997;89:853–4.
24. Kho KA, Nezhat C. Parasitic myomas. Obstet Gynecol. 2009;114:611–5.
25. Rabischong B, Beguinot M, Compan C, Bourdel N, Kaemmerlen AG, Pouly JL, Canis M, Mage G, Botchorishvili R. Long-term complication of laparoscopic uterine morcellation: iatrogenic parasitic myomas. J Gynecol Obstet Biol Reprod. 2013;42(6): 577–84.
26. Park JY, Park SK, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma. Gynecol Oncol. 2011;122(2):255–9.
27. Seidman MA, Oduyebo T, Muto MG, Crum CP, Nucci MR, Quade BJ. Peritoneal dissemination complicating morcellation of uterine mesenchymal neoplasms. PLoS One. 2012;7:11.
28. Nezhat C, Nezhat F, Bess O. Laparoscopically assisted myomectomy: a report of a new technique in 57 cases. Int J Fertil Menopausal Stud. 1994;39: 39–44.

29. Glasser MH. Minilaparotomy myomectomy: a minimally invasive alternative for the large fibroid. J Minim Invasive Gynecol. 2005;12(3):275–83.
30. Nezhat C, Nezhat F, Silfen SL, et al. Laparoscopic myomectomy. Int J Fertil. 1991;36:275–80.
31. Lethaby A, Vollenhoven B, Sowter M. Efficacy of preoperative gonadotrophin releasing hormone analogues for women with uterine fibroids undergoing hysterectomy or myomectomy: a systematic review. Br J Obstet Gynaecol. 2002;10(109):1097–108.
32. Campo S, Garcea N. Laparoscopic myomectomy in premenopausal women with and without preoperative treatment using gonadotrophinreleasing hormone analogues. Hum Reprod. 1999;19:44–8.
33. Freidman AJ, Rein NS, Harrison-Atlas D, et al. A randomized, placebocontrolled, double blind study evaluating leuprolide acetate depot treatment before myomectomy. Fertil Steril. 1989;52:728.
34. Vercellini P, Trespidi L, Zaina B, et al. Gonadotropin-releasing hormone agonist treatment before abdominal myomectomy: a controlled trial. Fertil Steril. 2003;79(6):1390–5.
35. Chen I, Motan T, Kiddoo D. Gonadotropin-releasing hormone agonist in laparoscopic myomectomy: systematic review and meta-analysis of randomized controlled trials. J Minim Invasive Gynecol. 2011;18:303–9.
36. Operative Laparoscopy Study Group. Postoperative adhesion developmentafter operative laparoscopy: evaluation at early second-look procedures. Fertil Steril. 1991;55:700.
37. Diamond MP. Reduction of adhesions after uterine myomectomy by Seprafilm membrance (HAL-F): a blinded, prospective, randomized, multicenter clinical study. Seprafilm Adhesion Study Group. Fertil Steril. 1996;66:904.
38. Mais V, Ajossa S, Piras B, Guerriero S, Marongiu D, Melis GB. Prevention of de-novo adhesion formation after laparoscopic myomectomy: a randomized trial to evaluate the effectiveness of an oxidized regenerated cellulose absorbable barrier. Hum Reprod. 1995;10(12):3133–5.
39. Ahmad G, Duffy JM, Farquhar C, Vail A, Vandekerckhove P, Watson A, Wiseman D. Barrier agents for adhesion prevention after gynaecological surgery. Cochrane Database Syst Rev. 2008;2, CD000475.
40. Watson A, Vandekerckhove P, Lilford R. Liquid and fluid agents for preventing adhesions after surgery for subfertility. Cochrane Database Syst Rev. 2000;(3):CD001298.
41. Linsky CB, Diamond MP, DiZerega GS. Effect of blood on the efficacy of barrier adhesion reduction in the rabbit uterine horn model. Infertility. 1998; 11:273.
42. Parker WH, Einarsson J, Istre O, Dubuisson JB. Risk factors for uterine rupture after laparoscopic myomectomy. J Minim Invasive Gynecol. 2010 Sep-Oct;17(5):551–4. J Minim Invasive Gynecol. 2010; 17(5):551–4.
43. Pistofidis G, Makrakis E, Balinakos P, Dimitriou E, Bardis N, Anaf V. Report of 7 uterine rupture cases after laparoscopic myomectomy: update of the update of the literature. J Minim Invasive Gynecol. 2012; 19(6):762–7.
44. Dubuisson JB, Chavet X, Chapron C, et al. Dubuisson JB, Chavet X, Chapron C, et al. Uterine rupture during pregnancy after laparoscopic myomectomy. Hum Reprod. 1995;10(6):1475–7.
45. Friedman W, Maier RE, Luttkus A, et al. Uterine rupture after laparoscopic myomectomy. Acta Obstet Gynecol Scand. 1996;75(7):683–4.
46. Malberti S, Ferrari L, Milani R. Spontaneous uterine rupture in the third trimester of gestation after laparoscopic myomectomy. A case report. Minerva Ginecol. 2004;56(5):479–80.
47. Cobellis L, Pecori E, Cobellis G, et al. Cobellis L, Pecori E, Cobellis G, et al. Comparison of intramural myomectomy scar after laparotomy or laparoscopy. Int J Gynaecol Obstet. 2004;84:87–8.
48. Weibel HS, Jarcevic R, Gagnon R, Tulandi T. Weibel HS, Jarcevic R, Gagnon R, Tulandi T. Perspectives of obstetricians on labour and delivery after abdominal or laparoscopic myomectomy. J Obstet Gynaecol Can. 2014;36(2):128–32.
49. Seidman DS, Nezhat CH, Nezhat F, Nezhat C. The Role of Laparoscopic-Assisted Myomectomy (LAM). JSLS. 2001;5:299–303.
50. Campo S, Campo V, Gambadauro P. Reproductive outcome before and after laparoscopic or abdominal myomectomy for subserous or intramural myomas. Eur J Obstet Gynecol Reprod Biol. 2003;110:215–9.
51. Kim MS, Uhm YK, Kim JY, Jee BC, Kim YB. Obstetric outcomes after uterine myomectomy: laparoscopic versus laparotomic approach. Obstet Gynecol Sci. 2013;56(6):375–81.
52. Metwally M, Cheong YC, Horne AW. Surgical treatment of fibroids for subfertility. Cochrane Database Syst Rev. 2012;(11):CD003857.
53. Soriano D, Dessolle L, Poncelet C, Benifla JL, Madelenat P, Darai E. Pregnancy outcome after laparoscopic and laparoconverted myomectomy. Eur J Obstet Gynecol Reprod Biol. 2003;108(2):194–8.
54. Jin C, Hu Y, Chen XC, Zheng FY, Lin F, Zhou K, Chen FD, Gu HZ. Laparoscopic versus open myomectomy–a meta-analysis of randomized controlled trials. Eur J Obstet Gynecol Reprod Biol. 2009;145(1):14–21.
55. Zhang Y, Hua KQ. Patients' age, myoma size, myoma location, and interval between myomectomy and pregnancy may influence the pregnancy rate and live birth rate after myomectomy. J Laparoendosc Adv Surg Tech A. 2014;24(2):95–9.
56. Sudik R, Husch K, Steller J, et al. Fertility and pregnancy outcome after myomectomy in sterility patients. Eur J Obstet Gynecol Reprod Biol. 1996;65:209–14.
57. Dessolle L, Soriano D, Poncelet C, et al. Determinants of pregnancy rate and obstetric outcome after laparoscopic myomectomy for infertility. Fertil Steril. 2001;76:370–4.

58. Olufowobi O, Sharif K, Papainnou S, et al. Olufowobi O, Sharif K, Papainnou S, et al. Are the anticipated benefits of myomectomy achieved in women of reproductive age? A 5-year review of the results at a UK tertiary hospital. J Obstet Gynaecol. 2004;24(4):434–40.
59. Marchionni M, Fambrini M, Zambelli V, et al. Reproductive performance before and after abdominal myomectomy (a retrospective analysis). Fertil Steril. 2004;82(82):154–9.
60. Seracchioli R, Rossi S, Govoni F, et al. Fertility and obstetric outcome after laparoscopic myomectomy of large myomata (a randomized comparison with abdominal myomectomy. Hum Reprod. 2000;15:2663–8.
61. Seracchioli R, Manuzzi L, Vianello F, Gualerzi B, Savelli L, Paradisi R, Venturoli S. Obstetric and delivery outcome of pregnancies achieved after laparoscopicmyomectomy. Fertil Steril. 2006;86(1):159–65.
62. Goldberg J, Pereira L, Berghella V, et al. Pregnancy outcomes after treatment for fibromyomata: uterine artery embolization versus laparoscopic myomectomy. Am J Obstet Gynecol. 2004;191(1):18–21.
63. Surrey ES, Minjarez DA, Stevens JM, et al. Effect of myomectomy on the outcome of assisted reproductive technologies. Fertil Steril. 2005;83(5):1473–9.
64. Oliveira FG, Abdelmassih VG, Diamond MP, et al. Impact of subserosal and intramural uterine fibroids that do not distort the endometrial cavity on the outcome of invitro fertilization–intracytoplasmic sperm injection. Fertil Steril. 2004;81(3):582–7.
65. Bernardi TS, Radosa MP, Weisheit A, Diebolder H, Schneider U, Schleussner E, Runnebaum IB. Laparoscopic myomectomy: a 6-year follow-up single-center cohort analysis of fertility and obstetric outcome measures. Arch Gynecol Obstet. 2014; 290:87–91.
66. Buttram VC, Reiter RC. Uterine leiomyomata: etiology, symptomatology and management. Fertil Steril. 1981;36:433–45.
67. Cooper NP, Okolo S. Fibroids in pregnancy – common but poorly understood. Obstet Gynecol Surv. 2005;60(2):132–8.
68. Yoo EH, Lee PI, Huh CY, Kim DH, Lee BS, Lee JK, Kim D. Predictors of leiomyoma recurrence after laparoscopic myomectomy. J Minim Invasive Gynecol. 2007;690.

Laparoscopic-Assisted Myomectomy

12

Camran Nezhat and Erika Balassiano

Introduction

Benign diseases of the uterus are encountered commonly in gynecologic practice and account for a large proportion of laparotomies and hysterectomies. Most of these procedures can be performed laparoscopically, with substantial advantages, for example: results equivalent to laparotomy, shorter hospitalization, decreased pain, faster recovery and financial savings. This chapter describes laparoscopic-assisted myomectomy (LAM). Nezhat et al. [1] developed LAM and reported on it in 1994. It has been advocated as a technique that retains the benefits of a laparoscopic procedure without the raised concerns of a complete laparoscopic myomectomy, namely, technically demanding procedure, prolonged anesthesia time, increased blood loss, possibly a higher risk of postoperative adhesion formation, and unprotected intracorporeal morcellation [2].

LAM allows rapid extra-abdominal morcellation of the myomas, which has gained wide acceptance due to the recent FDA statement discouraging the use of laparoscopic power intra-abdominal morcellation during hysterectomy or myomectomy for uterine fibroids [3, 4]. LAM avoids the risk of spreading an undiagnosed sarcoma and upstaging the malignancy. It also prevents iatrogenic formation of parasitic myomas and injury to intra-abdominal structures such as the bowel, bladder or pelvic vessels [5–14].

In carefully selected cases, LAM is a safe and efficient alternative to both laparoscopic myomectomy and myomectomy by laparotomy. These cases include patients with multiple large or deep intramural fibroids, such as in Fig. 12.1. In women who desire future pregnancies, LAM may be a better approach because it allows meticulous suturing of the uterine defect in multiple layers and thereby eliminates excessive electrocoagulation.

Fibroids

The most common solid pelvic tumors, fibroids affect approximately 20–25 % of women of reproductive age [15, 16]. They are result of

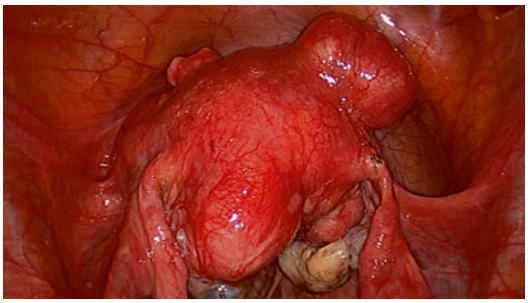

Fig. 12.1 Large, multiple leiomyomas

C. Nezhat, MD (✉) • E. Balassiano, MD
Center for Special Minimally Invasive and Robotic Surgery, Stanford University Medical Center, Stanford, CA, USA
e-mail: cnezhat@stanford.edu; erikabalassiano@gmail.com

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Table 12.1 Indications for myomectomy

Menometrorrhagia and anemia
Pelvic pain and pressure
Enlarging leiomyoma (greater than 12 weeks), inability to evaluate the adnexa and possibility of neoplasia
Associated fetal wastage and infertility
Obstructed ureter

benign transformation and proliferation of a single smooth muscle cell. The growth and development of myomas are influenced by many factors, some of which are not well defined. Increased estrogen stimulation, alone or synergistically with growth hormone or human placental lactogen, appears to be the major growth regulator. In contrast, progesterone appears to inhibit the growth of fibroids, although some evidence indicates that under certain circumstances it can promote their growth [17].

The severity of symptoms associated with uterine leiomyomas depends on the number of tumors, their size, and location. They may cause abdominal pressure, urinary frequency, constipation or alter blood flow to the uterus and endometrium, resulting in menorrhagia. Uterine leiomyomas are seldom the only cause of infertility, but data from several studies demonstrate a link between fibroids, fetal wastage, and premature delivery. The indications for treatment of fibroids are summarized in Table 12.1.

It is important to remember that uterine leiomyosarcomas are extremely difficult to differentiate from benign fibroids preoperatively. Screening techniques are limited, with endometrial biopsies being only 38–62 % accurate at its best [18]. Clinical factors, such as advancing patient age, enlarged uteri in a postmenopausal patient and a newly diagnosed uterine mass in the climaterium, should raise suspicion for malignancy [19]. Undiagnosed neoplasias render intra-abdominal morcellation extremely detrimental to the patient due to the risk of spreading carcinomatosis, and favor laparoscopic-assisted myomectomy with extraabdominal morcellation as the preferred approach.

Preoperative Evaluation

In women with menorrhagia, the hematocrit is used to assess the degree of anemia. Patients with large broad ligament fibroids may require an intravenous pyelogram to search for ureteral obstruction. Periodic pelvic and ultrasound examinations help monitor the growth rate of asymptomatic leiomyomas. Factors such as the size, number, and location of leiomyomas will influence the decision to perform a myomectomy by laparotomy or laparoscopy, or even hysterectomy. Submucous fibroids can be detected by ultrasound, hysterosalpingography, or hysteroscopy. Small intramural myomas may be palpated during laparotomy and missed at laparoscopy. Therefore, a vaginal ultrasound should be performed preoperatively [20, 21].

Laparoscopically Assisted Myomectomy (LAM), Laparoscopic Myomectomy (LM), and Myomectomy by Laparotomy

Patients with uterine myoma who desire future fertility present a challenge to most physicians attempting a laparoscopic approach. The risk of a future uterine rupture is a major concern following any operation involving the myometrium [22]. The difficulties of adequately closing all layers laparoscopically and using electrocoagulation for hemostasis may contribute to the risk of uterine rupture [23, 24].

Uteroperitoneal fistulas may follow laparoscopic myomectomy because meticulous laparoscopic approximation of all layers may be difficult. The use of electrocoagulation for hemostasis inside the uterine defect may also increase the risk of uteroperitoneal fistula formation. Postoperative adhesions increase when sutures are placed in the serosal layer [24, 25]. A single uterine incision for removal of multiple leiomyomas and subserosal approximation of the uterine defect is advised.

A combination of laparoscopy and minilaparotomy may reduce some of these problems.

The simpler procedure and reduced operative time will enable more gynecologists to apply this technique. The uterine closure also is improved when a mini- laparotomy is used for conventional suturing in two or three layers, thereby decreasing the possibility of uterine dehiscence, fistulas, and adhesions. The laparoscopic portion of the procedure allows the diagnosis and treatment of associated endometriosis or adhesions.

As a safe alternative to laparoscopic myomectomy (LM), laparoscopic-assisted myomectomy by mini-laparotomy (LAM) is a less technically difficult procedure and may require less time to complete. A decrease in operative time results from removing the myomas from the abdomen through a mini-laparotomy incision (see Fig. 12.2). Further, the risk of uterine rupture is lowered by suturing the uterine defect in layers and avoiding excessive electrocoagulation.

The decision to proceed with LAM usually is made in the operating room after the diagnostic laparoscopy and treatment of associated pathology are completed. The criteria for LAM are myoma greater than 5 cm or numerous myomas requiring extensive morcellation, deep intramural myoma, and removal that requires uterine repair with sutures in multiple layers.

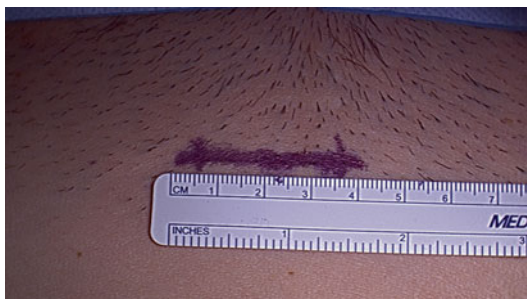

Fig. 12.2 Mini-laparotomy incision

To objectively compare the three techniques mentioned, charts from 143 patients who had either myomectomy by laparotomy (22; 15.3 %), LM (64; 44.7 %), or LAM (57; 39.8 %) were evaluated [22]. The 22 myomectomies by laparotomy were performed before the development of the LAM technique. The data are summarized (Table 12.2). The leiomyoma weight was greater in the LAM than LM group ($P < .05$). LAM replaced myomectomy by laparotomy, patient selection criteria were comparable, and the myoma weights of these two groups were similar.

The mean estimated blood loss of the LAM and laparotomy groups was not different. In contrast, blood loss among the LM patients was significantly lower and may be attributed to the smaller leiomyomas. Previous studies [25, 26] have underscored the need to decrease the operative time of LM. Although subserosal myomas less than 5 cm can be managed easily laparoscopically, larger and intramural lesions require prolonged morcellation and laparoscopic suturing of the uterine defect. The largest reported myomas removed by laparoscopy were 15–16 cm [25, 26] and one group reported that 10 cm was their limit [27]. Both laparoscopic morcellation and myometrial suturing may be difficult and can prolong operations. Laparoscopic morcellation has also

Table 12.2 Comparison of hysterectomy, abdominal myomectomy, and laparoscopic myomectomy for the management of symptomatic leiomyomas

	Hysterectomy	Abd myomectomy	LM
Degree of difficulty	Low	Moderate	High
Patient age	>45 years	Childbearing	>45 years
Recurrence (%)	None	10–15	10–15
Blood loss	<500 mL	Occasional >500 mL	<500 mL
Postop adhesion formation	Minimal	>30 %	>30 %
Postop hospitalization (days)	3–4	3–4	1–2
Type of myoma	All types	Intramural, subserosal, pedunculated	Subserosal, pedunculated
Uterine rupture	None	1 %	Risk of uteroperitoneal fistula

the risk of spreading an undiagnosed malignancy. LAM, with conventional morcellation and suturing through the mini-laparotomy incision, reduces the duration of the operation and the need for extensive laparoscopic experience. Similar mean operating times for LM and LAM techniques were observed despite larger myomas and their intramural positions, adjunctive laparoscopy, and the smaller incisions of the LAM group.

Hospitalization was longer for the patients who underwent myomectomy by laparotomy ($P < .05$) compared to both LAM and LM groups. When comparing the hospitalization time of the LAM and LM patients, the LAM group was longer ($P(LM) = .014$). This may be explained by the initial reluctance of some physicians to discharge LAM patients on the day of surgery or on the first postoperative day. After the initial 10–15 cases, all women underwent LAM on an outpatient basis. In fact, by removing the initial 15 cases from the LAM group, the mean hospital stay drops to 1.06 days, a time period not statistically different from the LM group.

The comparison of postoperative recovery time is important between the LAM and LM groups. Here, despite the differences in size and location of myoma, the recovery time can be compared because of the different incisions. The time elapsed before patients resumed work or regular activity is similar ($P > .05$). Introducing a 4-cm incision in the LAM group only slightly prolonged ($P > .05$) the subjectively perceived time for the women to achieve 100 % recovery.

Four major objectives of LAM are: minimizing blood loss, preventing postoperative adhesions, maintaining uterine wall integrity, and avoiding unprotected intracorporeal morcellation and its related complications.

Minimizing Blood Loss

Significant intraoperative blood loss can occur during the excision of subserosal and intramural leiomyomas. Depending on the tumor size and location, preoperative auto logous blood donation is suggested. Patients are counseled regarding the consequences of intraoperative and postoperative bleeding and the possible need for a laparotomy. For anemic patients, preoperative treatment with gonadotropin-releasing hormone (GnRH) may enable restoration of a normal hematocrit, decrease the size of the myoma [28] and reduce the need for transfusion [29] Intraoperatively, the use of dilute vasopressin helps to minimize blood loss. Vertical uterine incisions bleed less than transverse incisions [15] and pneumoperitoneum seems to decrease intraoperative bleeding.

Preventing Postoperative Adhesions

Although myomectomy is performed to preserve fertility, postoperative adhesion formation often jeopardizes this goal. Several procedures can minimize postoperative adhesions. Single, vertical, anterior, and midline uterine incisions are least to cause adhesions [30]. Although sutures predispose patients to adhesions, they are often necessary to close the uterine defect. While there are several adhesion barriers available or currently under development, none have proven effective [31, 32].

Maintaining Uterine Wall Integrity

Uterine rupture following myomectomy is rare, accounting for about 2 % of all pregnancy-related uterine ruptures [33]. Inadequate approximation of the uterine wall and poor healing [23] predispose patients for uterine rupture.

Avoiding Unprotected Intracorporeal Morcellation and Its Related Complications

Rates of visceral and vascular injury due to intracorporeal morcellation are difficult to determine due to under-reporting. Intracorporeal morcellation can also contribute for spreading an undiagnosed malignancy. The FDA estimates that one in every 350 women who have myomectomy have an unsuspected uterine sarcoma [34].

Second-look laparoscopies performed on post- myomectomy patients who had pedunculated and superficial subserosal myomas show complete uterine healing. In contrast, intramural and deep subserosal myomas are associated with evidence of granulation tissue and indentation of the uterus proportional to the size of the leiomyoma removed, unless sutures have been used to approximate the edges. The use of sutures is associated with a higher rate of adhesions. In patients with intramural fibroids and significant uterine wall defects, an unacceptably high rate of endometrial-serosal fistula formation occurs.

During an abdominal myomectomy, if the endometrial cavity is entered or a submucous myoma or large intramural myomas are removed, a patient who subsequently becomes pregnant should undergo a cesarean delivery [25]. Similar guidelines should be followed for laparoscopic myomectomies.

Preoperative Therapy with Gonadotropin-Releasing Hormone

Preoperative GnRH agonists have been used to decrease myomas and intraoperative blood loss [20, 35], simplify leiomyoma removal [36], and treat severe anemia [37]. However, despite some studies showing a decrease in intraoperative blood loss following a course of GnRH therapy [35] other studies do not [20]. GnRH therapy is expensive, associated with hypoestrogenic side effects [28] and possibly causes an increased risk of fibroid recurrence [20]. Preoperatively GnRH is indicated mainly to arrest menorrhagia and is given to women who can be managed with less invasive surgery such as hysteroscopic myomectomy.

LAM: Our Technique

The leiomyoma, or in cases of multiple myomas, the most prominent one, is injected at its base with 3–7 mL diluted vasopressin (see Fig. 12.3). A vertical incision is made over the uterine serosa until the capsule of the leiomyoma is reached.

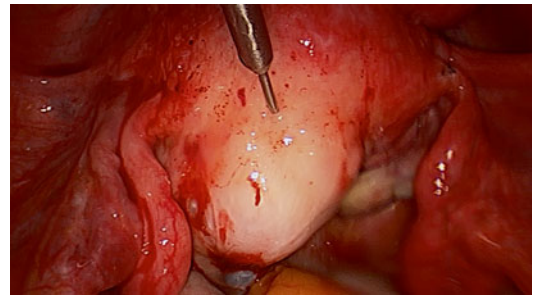

Fig. 12.3 Instillation of diluted vasopressin

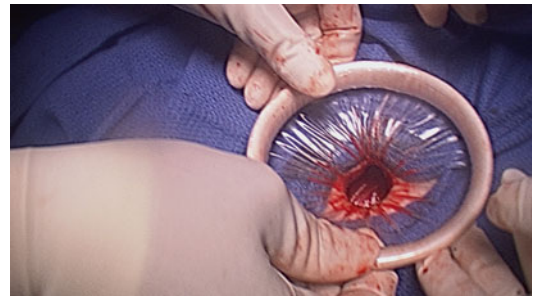

Fig. 12.4 Alexis retractor in place

A corkscrew manipulator is inserted into the leiomyoma and used to elevate the uterus toward the midline suprapubic puncture. With the trocar and manipulator attached to the myoma, this midline 5-mm puncture is enlarged to 4–5 cm transverse incision. Following the incision of the fascia transversely at 3–5 cm, the rectus muscles are separated at the midline. The peritoneum is entered transversely and an Alexis self-retaining retractor is inserted into the abdomen for excellent exposure (Fig. 12.4).

The leiomyoma is located and brought to the resulting incision using the corkscrew manipulator. The uterine manipulator is used to raise the uterus. The corkscrew manipulator is replaced with two Lahey tenacula and attempt is made to remove the leiomyoma intact. Large specimens can be shelled sequentially at the level of the skin incision after the specimen is placed inside a bag and brought to the mini-laparotomy incision (Fig. 12.5). Then, the fibroid is gradually morcellated with the scalpel outside the abdomen while exposing new areas (Fig. 12.6).

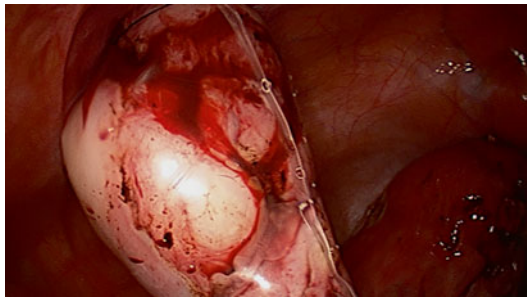

Fig. 12.5 Fibroids safely removed in a bag

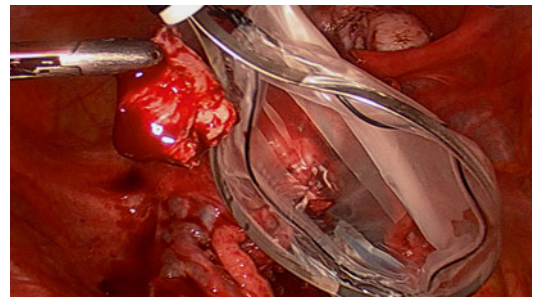

Fig. 12.7 Fibroids safely removed a bag

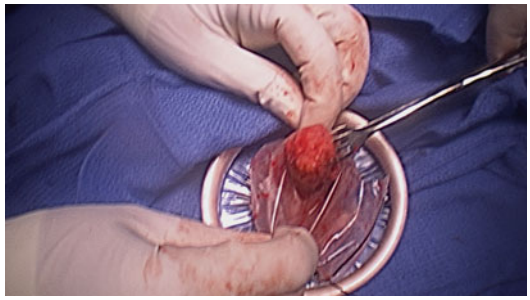

Fig. 12.6 Extra corporeal morcellation

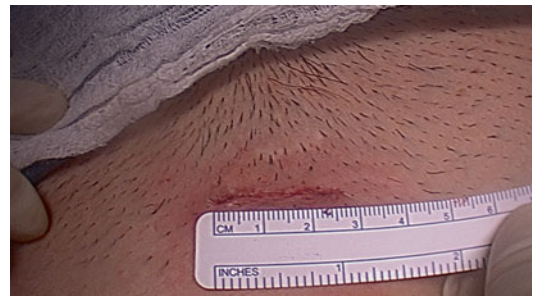

Fig. 12.8 Mini-laparotomy incision after subcuticular closure

After complete removal of the leiomyoma, the uterine wall defect is seen through the incision. If uterine size allows, the uterus is brought to the skin through the mini-laparotomy incision to complete the repair. When multiple leiomyomas are found, as many as possible are removed through a single uterine incision. When the leiomyomas are in distant locations and identification is impossible, the mini-laparotomy incision is closed temporarily by twisting the Alexis retractor. The laparoscope is reintroduced, and the leiomyomas identified and brought to the incision inside a bag for extra-abdominal morcellation (Fig. 12.7). Posterior leiomyomas may be difficult to reach with the minilaparotomy incision and are removed completely laparoscopically, allowing exteriorization of the uterus through the mini-laparotomy incision.

The uterus is reconstructed in layers using 4–0 to 2–0 and O polydioxanone suture without suturing the serosa and the uterus is palpated to insure that there are no small intramural leiomyomas. The uterus is returned to the peritoneal cavity, and the fascia and skin are closed in layers. The fascia is closed with 1–0 polyglactin suture and the skin is closed in a subcuticular manner. The laparoscope is used to evaluate the uterus and ensure final hemostasis. At this time, the pelvis is evaluated to detect and treat endometriosis and adhesions that may have been obscured previously by large leiomyomas. Copious irrigation is performed, blood clots are removed, and Interceed is applied over the uterus to help prevent adhesion formation. Figure 12.8 demonstrates the mini-laparotomy incision after subcuticular closure was completed.

Women are observed postoperatively for possible complications. A complete blood count is obtained the day of or following surgery. When the women awaken, an oral medication is prescribed for pain. In the developmental stages of this procedure, myomectomy patients were admitted to the hospital so that their postoperative course could be monitored closely. Currently, patients are allowed to leave the afternoon or evening of surgery provided their condition is stable.

Recommendations

Several concerns must be addressed before laparoscopic myomectomy will be accepted in place of laparotomy. Uterine healing and the extent of adhesion formation associated with laparotomy must be compared with the laparoscopic approach in which sutures are used. Women of childbearing age who require a myomectomy should undergo either an abdominal myomectomy, a modified laparoscopic procedure (LAM), or laparoscopic myomectomy with protected intracorporeal morcellation ensuring proper closure of the myometrial defect.

References

1. Nezhat C, Nezhat F, Bess O, Nezhat CH, Mashiach R. Laparoscopically assisted myomectomy: a report of a new technique in 57 cases. Int J Fertil Menopausal Stud. 1994;39(1):39–44.
2. Seidman DS, Nezhat CH, Nezhat F, Nezhat C. The role of laparoscopic-assisted myomectomy (LAM). JSLS. 2001;5:299–303.
3. Kho KA, Nezhat CH. Evaluating the risks of electric uterine morcellation. JAMA. 2014;311:905–6. doi:10.1001/jama.2014.1093.
4. Hampton T. Critics of fibroid removal procedure question risks it may pose for women with undetected uterine cancer. JAMA. 2014;311:891–3.
5. Milad MP, Milad EA. Laparoscopic morcellator-related complications. J Minim Invasive Gynecol. 2014;21:486–91. pii: S1553-4650(13)01434-9.
6. Sizzi O, Rossetti A, Malzoni M, Minelli L, La Grotta F, Soranna L, Panunzi S, Spagnolo R, Imperato F, Landi S, Fiaccamento A, Stola E. Italian multicenter study on complications of laparoscopic myomectomy. J Minim Invasive Gynecol. 2007;14(4):453–62.
7. Nezhat C, Kho K. Iatrogenic myomas: new class of myomas? J Minim Invasive Gynecol. 2010;17(5):544–50.
8. Pezzuto A, Serboli G, Ceccaroni M, Ferrari B, Nardelli GB, Minelli LL. Two case reports of bowel leiomyomas and review of literature. Gynecol Endocrinol. 2010;26(12):894–6.
9. Miyake T, Enomoto T, Ueda Y, Ikuma K, Morii E, Matsuzaki S, Murata Y. A case of disseminated peritoneal leiomyomatosis developing after laparoscope-assisted myomectomy. Gynecol Obstet Invest. 2009; 67(2):96–102.
10. Oduyebo T, Rauh-Hain AJ, Meserve EE, Seidman MA, Hinchcliff E, George S, Quade B, Nucci MR, Del Carmen MG, Muto MG. The value of re-exploration in patients with inadvertently morcellated uterine sarcoma. Gynecol Oncol. 2014;132(2):360–5.
11. Seidman MA, Oduyebo T, Muto MG, Crum CP, Nucci MR, Quade BJ. Peritoneal dissemination complicating morcellation of uterine mesenchymal neoplasms. PLoS One. 2012;7(11):e50058.
12. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. The impact of tumor morcellation during surgery on the outcomes of patients with apparently early low-grade endometrial stromal sarcoma of the uterus. Ann Surg Oncol. 2011;18(12):3453–61.
13. Della Badia C, Karini H. Endometrial stromal sarcoma diagnosed after uterine morcellation in laparoscopic supracervical hysterectomy. J Minim Invasive Gynecol. 2010;17(6):791–3.
14. Anupama R, Ahmad SZ, Kuriakose S, Vijaykumar DK, Pavithran K, Seethalekshmy NV. Disseminated peritoneal leiomyosarcomas after laparoscopic "myomectomy" and morcellation. J Minim Invasive Gynecol. 2011;18(3):386–9. 10.
15. Buttram VC, Reiter RC. Uterine leiomyomata: etiology symptomatology and management. Fertil Steril. 1981;556:433.
16. Vollenhoven BJ, Lawrence AS, Healy DL. Uterine fibroids: a clinical review. Br J Obstet Gynaecol. 1990;97:285.
17. Cramer SF, Robertson AL, Ziats NP, et al. Growth potential of human uterine leiomyomas: some in vitro observations and their implications. Obstet Gynecol. 1990;97:393.
18. Bansal N, Herzog TJ, Burke W, Cohen CJ, Wright JD. The utility of preoperative endometrial sampling for the detection of uterine sarcomas. Gynecol Oncol. 2008;110(1):43.
19. Cohen, S. The morcellation debate: what you need to know. Contemporary Ob/Gyn. March, 2014:30–9.
20. Fedele L, Vercellini P, Bianchi S, et al. Treatment with GnRH agonists before myomectomy and the risk of short-term myoma recurrence. Br J Obstet Gynaecol. 1990;97:393.
21. Fedele L, Bianchi S, Dorta M. Transvaginal ultrasonography versus hysteroscopy in the diagnosis of uterine submucous myomas. Obstet Gynecol. 1991;77: 745–8.
22. Nezhat CR, Nezhat F, Bess O, et al. Laparoscopically assisted myomectomy: a comparison of a new technique to myomectomy by laparotomy and laparoscopy. Int J Fertil. 1994;39:39.
23. Harris WJ. Uterine dehiscence following laparoscopic myomectomy. Obstet Gynecol. 1992;80:545–6.
24. Nezhat CR, Nezhat F. Laparoscopic myomectomy complications. Int J Fertil. 1991;37:64. Letter.
25. Nezhat C, Nezhat F, Silfen SL, et al. Laparoscopic myomectomy. Int J Fertil. 1991;36:275–80.
26. Hasson HM, Rotman C, Rana N, et al. Laparoscopic myomectomy. Obstet Gynecol. 1992;80:884–8.
27. Dubuisson JB, Lecuru F, Herve F, et al. Myomectomy by laparoscopy. Fertil Steril. 1991;56:827–30.

28. Friedman AJ, Rein NS, Harrison-Atlas D, et al. A randomized, placebo-controlled, double blind study evaluating leuprolide acetate depot treatment before myomectomy. Fertil Steril. 1989;52:728.
29. Shaw RW. Mechanism of LHRH analogue action in uterine fibroids. Horm Res. 1989;32:150.
30. Operative Laparoscopy Study Group. Postoperative adhesion development after operative laparoscopy: evaluation at early second- look procedures. Fertil Steril. 1991;55:700–4.
31. Linsky CB, Diamond MP, DiZerega GS. Effect of blood on the efficacy of barrier adhesion reduction in the rabbit uterine hormonal model. Infertility. 1988;11:273.
32. Bayers SP, Jansen D. Gore—Tex surgical membrane. In: DeChemey A, Diamond MP, editors. Treatment of post-surgical adhesions. New York: Wiley Liss; 1990. p. 293.
33. Georgakopoulous PA, Bersis G. Sigmoido-uterine rupture in pregnancy after multiple myomectomy. Int Surg. 1981;66:367–8.
34. Motluk A. FDA discourages use of tissue-shredding tool – device may contribute to cancer spread after fibroid surgery. Nature News. April, 2014. doi: 10.1038/nature.2014.15085
35. Lumsden MA, West GP, Baird DT. Goserelin therapy before surgery for uterine fibroids. Lancet. 1987; 1:36.
36. Rock JA. Gonadotropin-releasing hormone agonist analogs in the treatment of uterine leiomyomas. J Gynecol Surg. 1991;7:147.
37. George M, Lhomme C, Lefort J, et al. Long-term use of an LH-RH agonist in the management of uterine leiomyomas a study of 17 cases. Int J Fertil. 1989; 34:19.

Robot-Assisted Myomectomy: Broadening the Laparoscopist's Armamentarium

13

Antonio R. Gargiulo and Ceana Nezhat

Multiple randomized controlled trials (RCTs) and at least one meta-analysis demonstrate the clinical advantages of laparoscopic myomectomy (LM) over abdominal myomectomy [1–7]. Such advantages include reduced overall complications, blood loss, hemoglobin drop, postoperative pain and length of hospital stay, as well as faster recovery. Two of the RCTs [4–5] show equivalent cumulative pregnancy and live birth rates, with an advantage of the laparoscopic approach even over mini laparotomy in patients without infertility undergoing surgery for symptomatic leiomyomas [4].

The reported rate of uterine rupture in pregnancies following LM is between 0 and 0.25 %, which is similar to the rate observed following a lower uterine segment cesarean section (0.32 %) and compares favorably to the rate of uterine rupture following AM, which ranges from 0 to 4 % [5, 8–11]. A multicenter study examining the obstetric outcomes of women who conceived after robotic myomectomy (RM) reported a 1.1 % incidence of uterine rupture, which is well within the expected range [12]. This single incident was associated with use of monopolar electrosurgery during myomectomy. It is helpful to point out that the use of electrocautery seems to be common to a disproportionate number of uterine ruptures reported in the literature following minimally invasive myomectomy [10]. Even though studies are not yet available to define which energy tool has the best overall clinical outcome in minimally invasive myomectomy, alternatives energy instruments associated with less thermal spread (such as ultrasonic and laser) should be considered where future childbearing is expected.

All things considered, there is strong evidence to suggest that myomectomy should be performed by laparoscopy whenever this is technically possible. This simple concept is, in our view, the nodal point of the entire argument in favor of robotic assistance as an important complementary technique in the armamentarium of the minimally invasive gynecologic surgeon. That is because conventional LM is a technically demanding procedure that remains underutilized. According to a recent survey, only 3.1 % of Canadian gynecologists perform myomectomy by laparoscopy in over 50 % of cases, and over

A.R. Gargiulo, MD (✉)
Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
e-mail: agargiulo@partners.org

C. Nezhat, MD, Prof, FACOG, FACS
Department of Gynecology and Obstetrics, Emory University, School of Medicine, Atlanta, GA, USA

Departments of Obstetrics, Gynecology and Surgery, Stanford University Medical Center, Stanford, CA, USA

Nezhat Medical Center for Special Minimally Invasive Surgery and Reproductive Medicine, Atlanta, GA, USA
e-mail: ceana@nezhat.com

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75 % do not offer it at all [13]. A similar study on practice preferences of American surgeons regarding abdominal versus laparoscopic and vaginal hysterectomy shows similar results (on an operation whose complexity does not come close to that of myomectomy) [14]. This data highlight the need for a radical educational or technological breakthrough to improve patients' access to minimally invasive surgery. Meanwhile, abdominal myomectomy remains the standard of care in most developed countries [15]. Of course, not all myomectomies can be laparoscopic: every surgical team will have a threshold of myoma size, number and location, as well as a threshold of patient typology, beyond which they will have to resort to the abdominal approach. The ability of gynecologists to push the envelope of minimally invasive surgery has been increasing (alas at a slow pace) in parallel with technological innovation. We propose that, given the technology currently at our disposal, the threshold for abdominal myomectomy can become substantially higher than what is suggested in the study by Liu et al. Indeed, the technological armamentarium available to many minimally invasive gynecologic surgeons has included computer-assisted teleoperators (popularly known as surgical robots) for abut a decade. These powerful technical enhancers can heighten any surgical team's threshold for open surgery. Although no RCTs have ever been designed to prove this simple concept, these authors (who have a combined experience of both laparoscopic and robotic myomectomy numbering in more decades that we care to admit) hold it as self-evident. Having a choice, when planning a minimally invasive myomectomy, we opt for robotic assistance if a complex scenario is expected.

We know that RM is a safe and reproducible procedure, with outcomes that mirror those of traditional laparoscopy. Advincula and colleagues introduced the procedure in 2004 [16]. Since then, multiple retrospective cohort studies have confirmed its safety and efficacy [17–21]. Case-matched comparisons between patients undergoing AM or RM show that RM is associated with lower mean blood loss, fewer complications and shorter hospital stay while it requires significantly longer operative time [6, 18, 22]. Nezhat et al. and Bedient et al. independently compared RM and LM and revealed no significant differences in short-term outcomes between the two procedures [19, 21]. Similarly, Barakat et al. found no significant differences between LM and RM in terms of blood loss, operative time, or hospital stay despite a significantly larger tumor load in the RM group (223 vs. 97 g, $p<0.001$), which suggests that the surgeons opted for robotic assistance in cases where a larger tumor load was expected. In the same study, hospital stay, blood loss, and hemoglobin drop were all significantly reduced in RM compared to AM despite a similar tumor load. The authors concluded that RM improves utilization of a minimally invasive approach to myomectomy [18].

Gargiulo et al. compared short-term outcomes from 174 RM and 115 LM respectively performed by two separate reproductive high-volume surgical teams [20]. The tumor load was similar for the two groups. Perioperative outcomes were excellent for both techniques and no conversions to open surgery occurred in either group. Median operative time was longer for RM (191 min vs. 115 min). However, barbed suture was used in most LM cases but only in 5 % of RM and may have contributed to the observed difference in operative time.

In conclusion, a growing body of literature suggests that abdominal myomectomy should no longer represent the standard of care for conservative surgical treatment of uterine fibroids. Rather, all forms of minimally invasive access should be considered first. However, the guiding principles of a myomectomy cannot change depending on the surgical modality. Laparoscopic myomectomy should always be a technically uncompromised replica of traditional open microsurgical myomectomy. As such, LM is a technically demanding operation that is still committed to a limited adoption at almost 25 years from its introduction [23]. Indeed, every laparoscopic surgeon has a personal safety threshold for resorting to open surgery. By raising such laparotomy threshold, RM may replace AM in many instances.

Robot-Assisted Myomectomy: Technique in Images

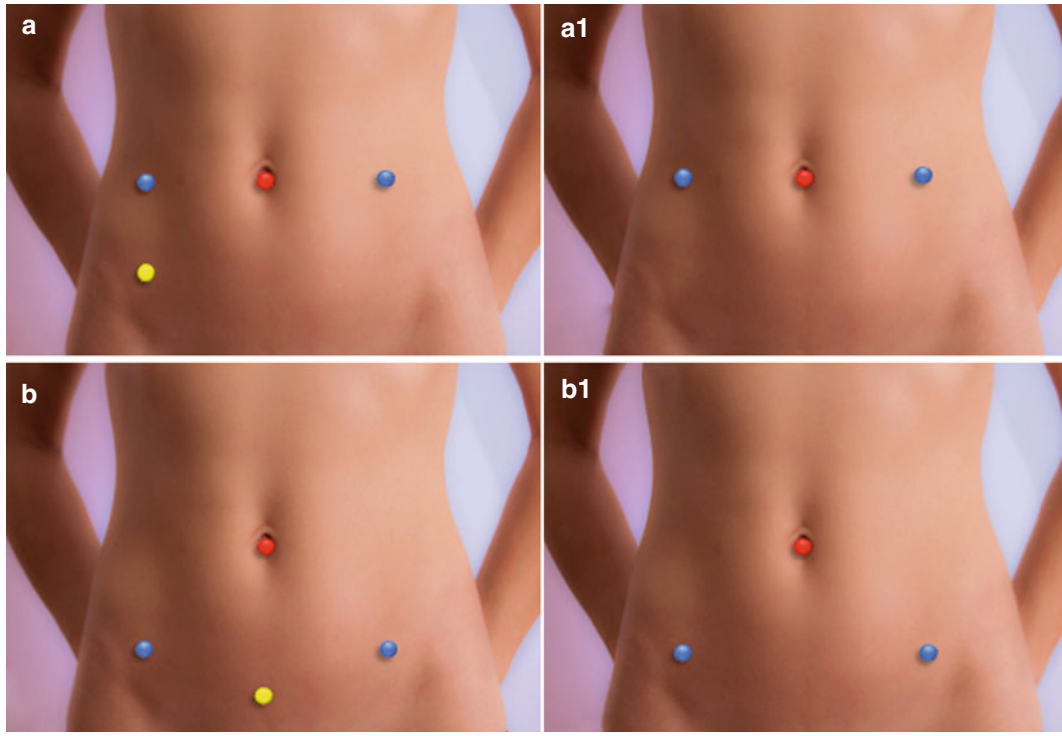

Fig. 13.1 Laparoscopic port placement for robot-assisted myomectomy: standard protocol (pictures **a**, **a1**). The camera port is umbilical. Robotic arm ports 1 and 2 are between 8 and 10 cm to the left and to the right of the umbilicus. The assistant port is medial to the anterior-superior iliac spine (either left or right side). It is possible to forgo the assistant port as the team's experience increases: needles can be inserted through the camera port and suction can be provided through a robotic port without any need for undocking. Robotic arm port 3 should be used for more complex cases: it is placed contra-laterally to the assistant's port. This entire configuration is shifted cephalad to address larger uterine masses. Laparoscopic port placement for robot-assisted myomectomy: minimal access protocol (pictures **b**, **b1**). This is an advanced protocol: no scars are visible above the anterior-superior iliac spines, however the robotic instruments enter the pelvic at a wider angle from the midline and are more difficult to handle. The camera port is umbilical. Robotic arm ports 1 and 2 are medial to the anterior-superior iliac spines. There is no room for robotic arm port 3. The assistant port is suprapubic (or absent, see considerations for standard protocol)

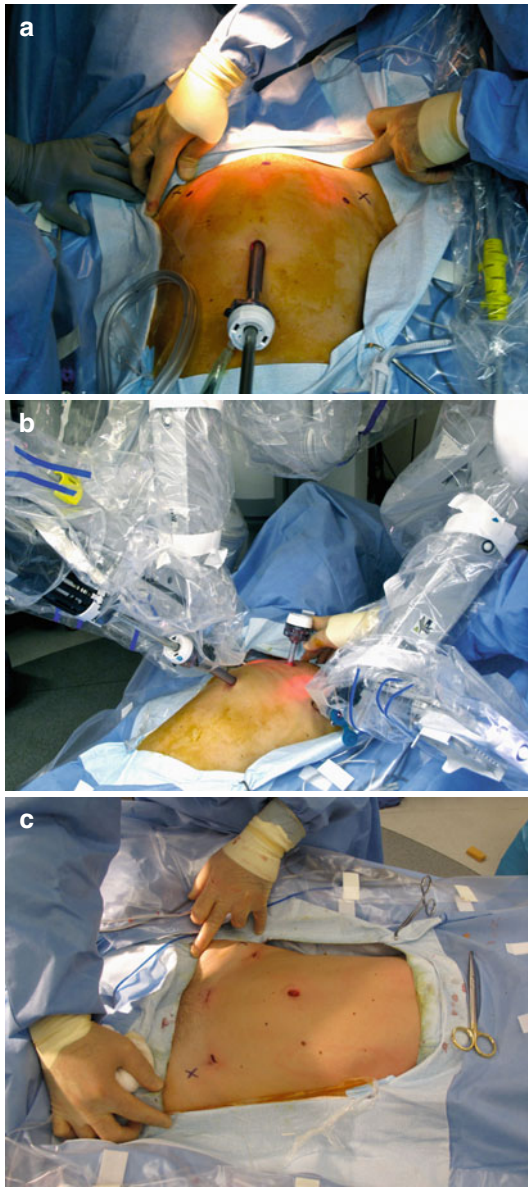

Fig. 13.2 Actual surgical images of patient operated with a minimal access (cosmetic) protocol. (**a**) Planning of port sites with distended abdomen. Note that port sites are slightly cephalad to the anterior-superiod iliac spines to avoid injury of the ileoinguinal and ileohypogastric nerves. (**b**) Ample space is created in the suprapubic area for the assistant to use the suprapubic access. (**c**) Final postoperative effect

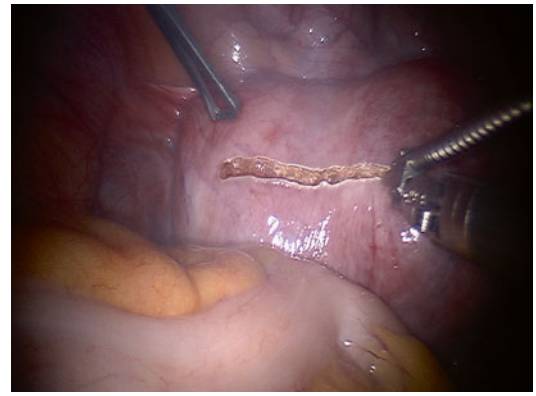

Fig. 13.3 Hysterotomy. This can be performed in a transverse, sagittal or elliptical fashion, depending on myoma location and size and surgeon's preference. In this particular case a flexible CO2 laser delivery system (BeamPath™, OmniGuide, Cambridge, MA) connected to a robotic needle driver is employed. This setup allows full use of the wristing ability of the robotic instruments. Robotic Harmonic sheers are an excellent alternative and also provide minimal thermal spread and therefore minimal myometrial damage. A drawback of the robotic Harmonic sheers is that the long vibrating element does not allow any movement of the wrist, thereby limiting the ergonomic advantage of the robotic platform. Use of robotic monopolar sheers, albeit very popular, is the least appropriate for reproductive surgery applications, including myomectomy. If robotic monopolar shears are employed, one should do so with exclusive cutting – not coagulating – current settings

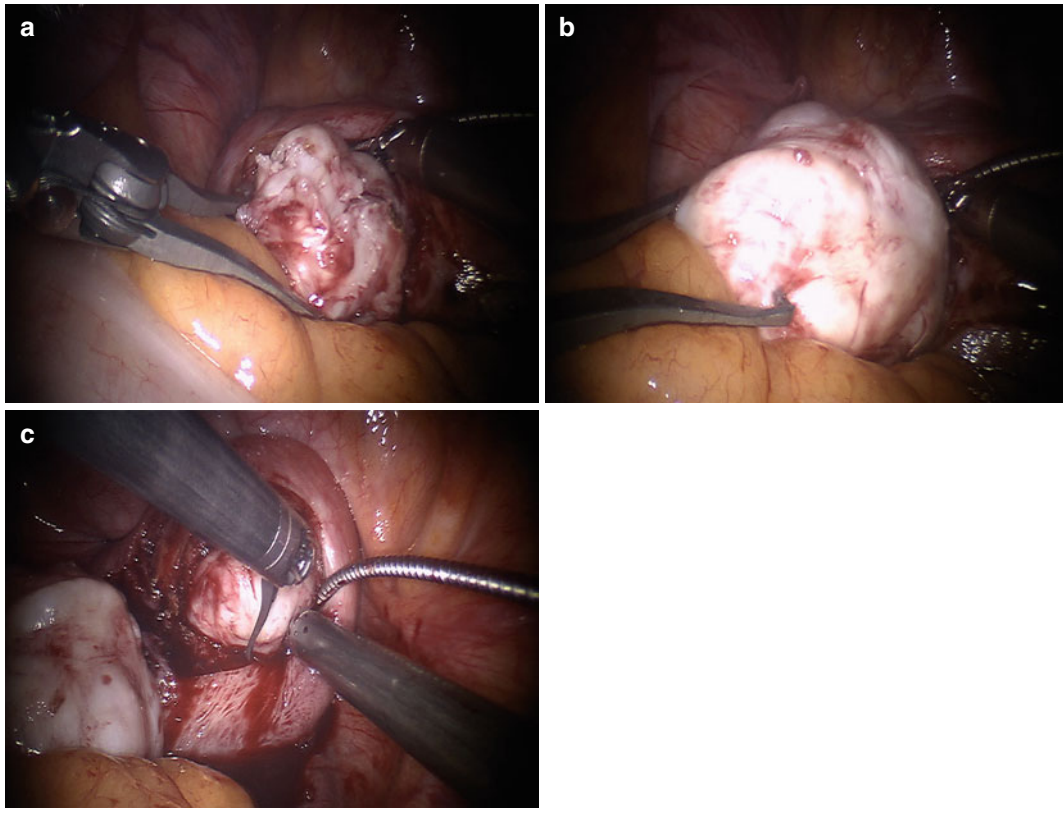

Fig. 13.4 Myoma enucleation. The goals of myoma enucleation are: (1) reduce the number of hysterotomies needed for enucleation of all myomas, and (2) avoid injury to the endometrial cavity and the tubal lumen. Once the space between the pseudocapsule and the tumor is entered with use of energy, dissection continues in a blunt fashion for most of the myoma enucleation. The robotic tenaculum is not designed to pull the myoma out of its pseudocapsule: rather it is used to steady the tumor while other instruments make progress in detaching the pseudocapsule from it. Some areas of the pseudocapsule are tightly connected to the myoma and may require focal energy use, rather than blunt dissection, to complete the least traumatic enucleation. We perform chromopertubation in advance of any myomectomy where breach of the endometrial cavity is a possibility. Chromopertubation is not done to assess tubal patency, as this has minimal relevance and has little predictive value on future tubal function, but to stain the endometrial cavity and make it easy to identify an entry. (**a**) Robotic tenaculum stabilizes the myoma and instrument 1 opposes counter-traction to facilitate enucleation. (**b**) Enucleation almost complete. (**c**) A second myoma is removed through the same incision: economy of incisions is a key factor in every myomectomy

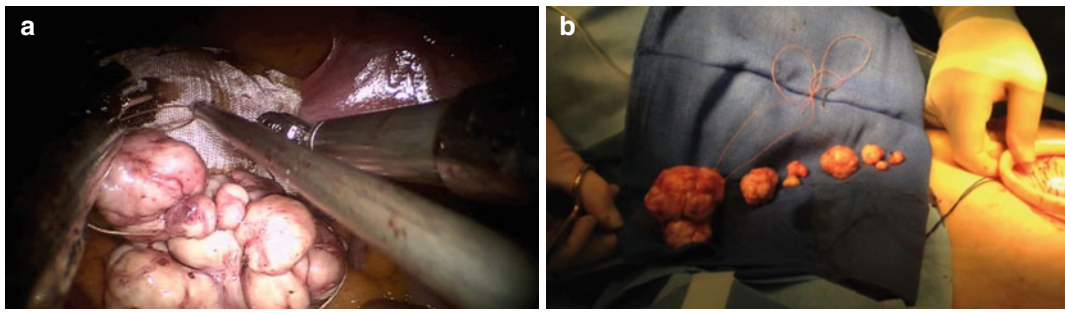

Fig. 13.5 Myoma string. In cases where many small myomas are enucleated, we keep a written myoma count at bedside and we collect those myomata that could be lost in the abdomen on a suture line. A barbed suture is particularly helpful for this task, as myomas can be made to slide towards the loop end of the suture and cannot slide back. A suture life-line is also helpful to keep the myomas collected for later placement in a containment system (see Fig. 13.7 below). (**a**) Several small myomas on a string (coaxial single-incision robot-assisted myomectomy). (**b**) Same patient with myomata recovered through single umbilical incision

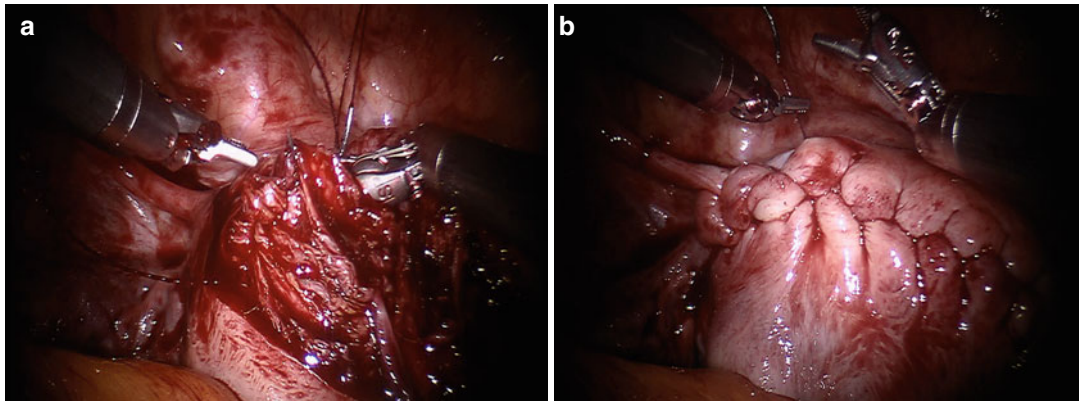

Fig. 13.6 Repair of hysterotomy in layers. The goals of hysterotomy closure are: (1) anatomically correct reapproximation of all layers, (2) mechanical control of hemostasis and avoidance of hematoma formation, and (3) avoidance of exposed suture, exposed myometrium and coagulated serosa (highly adhesiogenic foci). The suture of choice for myomectomy is barbed suture. Deep layers are closed in a simple running fashion and the final layer (perimetrium ad serosa together) is closed with a running non-locking imbricating "baseball stitch" suture. A well performed baseball stitch will have no barbed suture visible and constitutes a safe and highly hemostatic closure. Occasionally, we employ 3.0 or 2.0 non-barbed suture to reapproximate an endometrial laceration or a small superficial hysterotomy. (**a**) Closure in several layers is essential to avoid hematoma formation. (**b**) Baseball stitch demonstrating no visible barbed suture

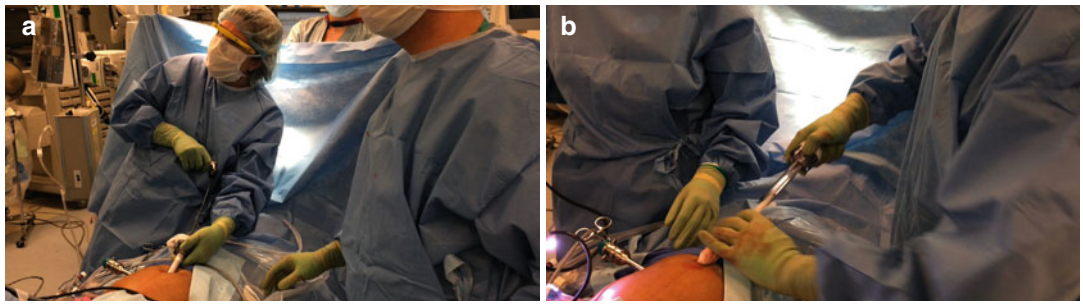

Fig. 13.7 Morcellation. This step is not performed with robotic assistance but rather with conventional technique. Electromechanical morcellation of myomas in the abdominal cavity remains a viable option for myoma extraction following minimally invasive myomectomy, provided patients are duly informed of the underlying risk of unintended morcellation of a malignant tumor. In those cases where the benign histologic nature of the myoma is in doubt, morcellation in a containment system should be considered to virtually eliminate the risk of tumor dispersion in the abdominal cavity. Electromechanical laparoscopic morcellation can be safely performed within a containment system. (**a**) Laparoscopic sac is placed through a 15 mm umbilical port. (**b**) After myomas are placed in the bag, the 15 mm port is removed. (**c**) The 15 mm port is re-inserted, this time inside the laparoscopic sac; the sac is insufflated. (**d**) A 5 mm camera port is inserted in place of one of the robotic instrument ports; the camera port pierces the sac and its pneumatic fixation tip is insufflated. (**e**) The pneumatic fixation tip of the 5 mm port is insufflated and in place within the insufflated specimen sac. (**f**) The laparoscope is now inserted through the 5 mm port, so that the 15 mm port can be removed again. (**g**) The morcellator is set in place of the 15 mm port. (**h**) Morcellation proceeds in a completely contained system. (**i–j**) The laparoscopic sac is removed and examined to confirm that it is intact. (**k**) An identical technique can be used for morcellation through a lower quadrant port if preferred

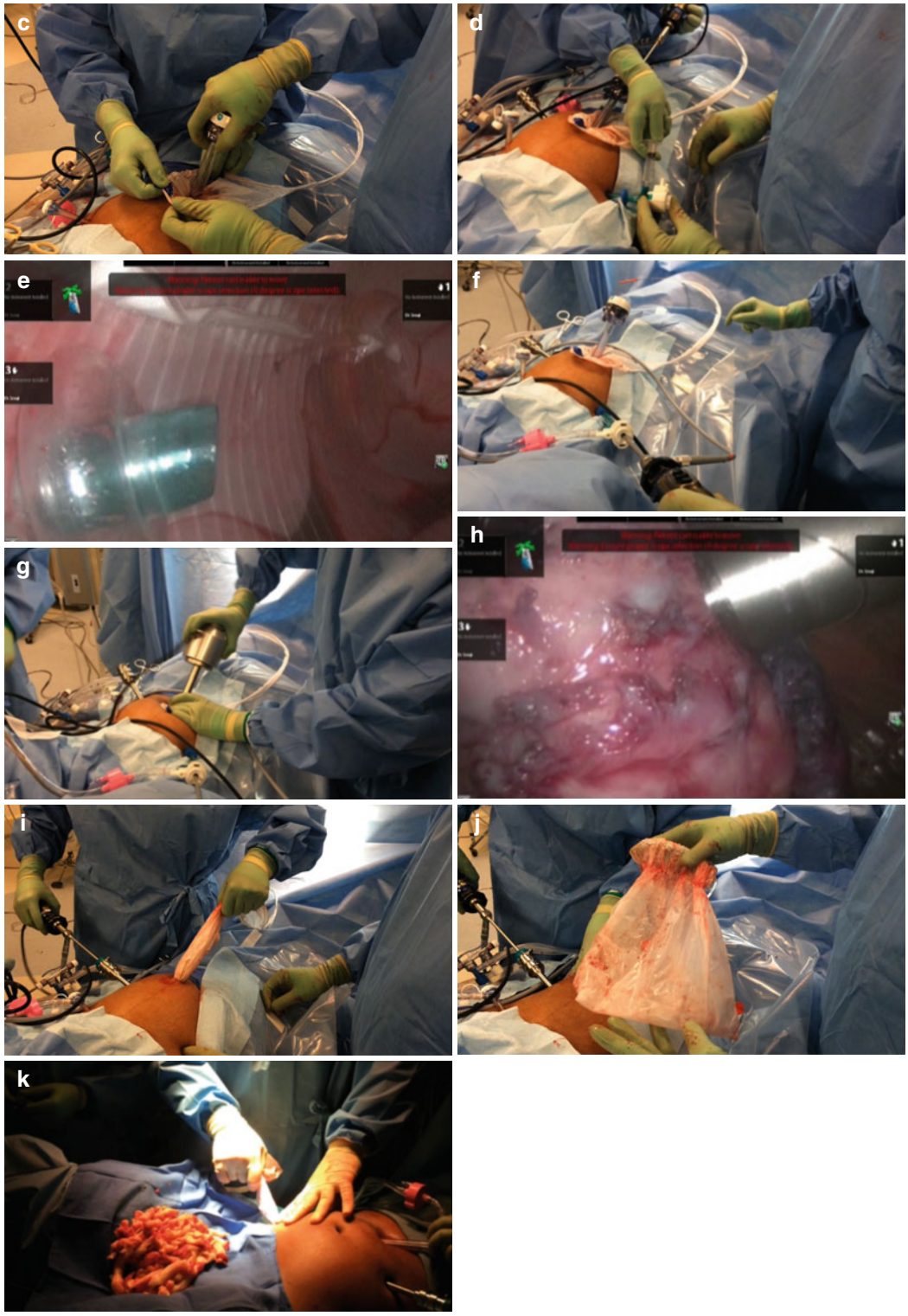

Fig. 13.7 (continued)

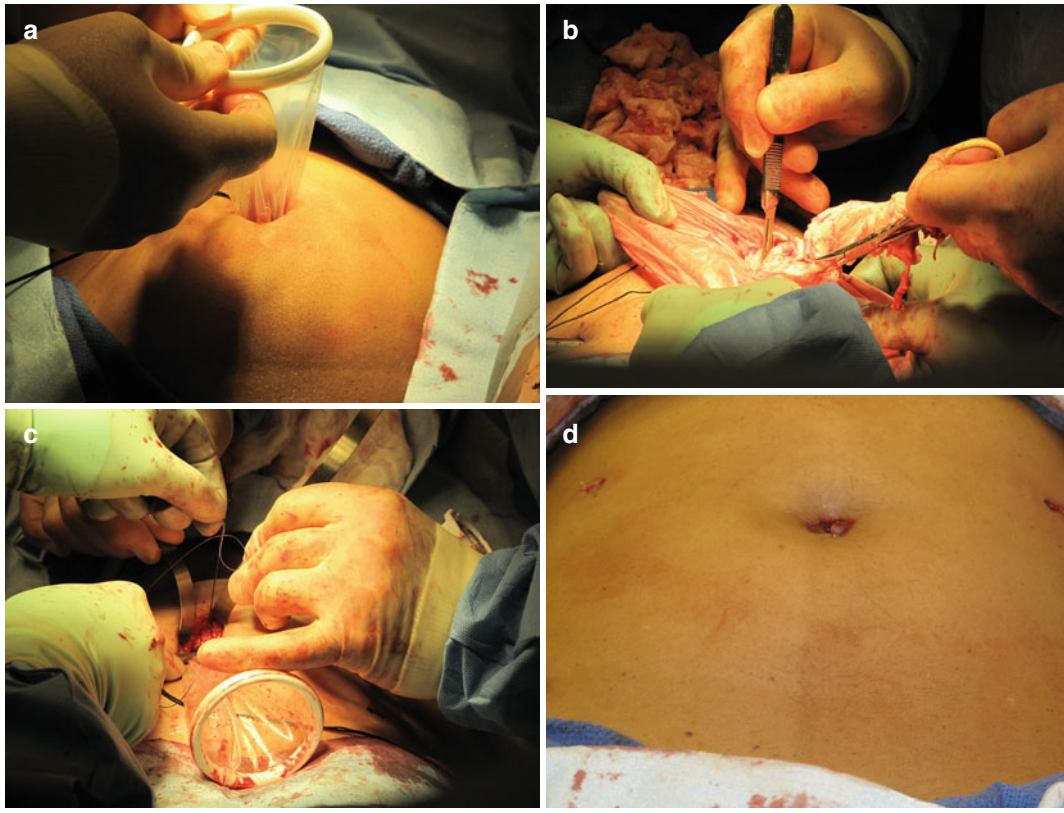

Fig. 13.8 Some patients and surgeons may prefer manual morcellation. This can also be achieved with excellent cosmetic results employing a single incision laparoscopy port to be used as a small minilaparotomy at the end of the procedure. We have had experience with both suprapubic and umbilical placement of these minilaparotomy ports. (**a**) Umbilical placement of GelPoint Mini (Applied Medical, Inc) single incision laparoscopy device. (**b**) Large myoma is morcellated with #10 blades and towel clips. (**c**) Repair of the fascia with several interrupted figure-of-eight stitches. (**d**) Exceptionally diminutive incision within the umbilical scar (a 540 g myoma was morcellated through this incision). (**e**) Suprapubic placement of GelPoint Mini. (**f**) The laparoscopic sac containing the myomata is exteriorized. (**g**) A technique that is identical to that illustrated above is employed

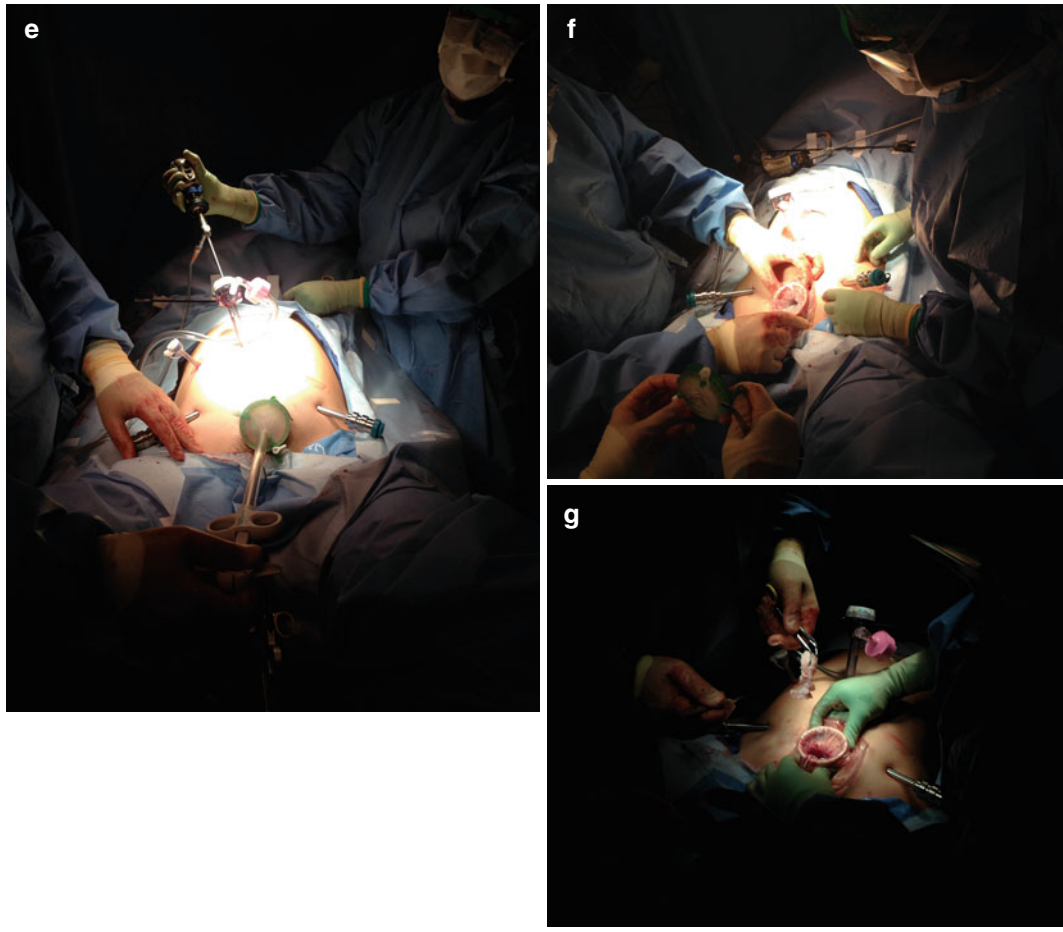

Fig. 13.8 (continued)

References

1. Alessandri F, Lijoi D, Mistrangelo E, Ferrero S, Ragni N. Randomized study of laparoscopic versus minilaparotomic myomectomy for uterine myomas. J Minim Invasive Gynecol. 2006;13:92–7.
2. Cicinelli E, Tinelli R, Colafiglio G, Saliani N. Laparoscopy vs minilaparotomy in women with symptomatic uterine myomas: a prospective randomized study. J Minim Invasive Gynecol. 2009; 16:422–6.
3. Fanfani F, Fagotti A, Bifulco G, Ercoli A, Malzoni M, Scambia G. A prospective study of laparoscopy versus minilaparotomy in the treatment of uterine myomas. J Minim Invasive Gynecol. 2005;12: 470–4.
4. Palomba S, Zupi E, Falbo A, et al. A multicenter randomized, controlled study comparing laparoscopic versus minilaparotomic myomectomy: reproductive outcomes. Fertil Steril. 2007;88:933–41.
5. Seracchioli R, Manuzzi L, Vianello F, et al. Obstetric and delivery outcome of pregnancies achieved after laparoscopic myomectomy. Fertil Steril. 2006;86: 159–65.
6. Mais V, Ajossa S, Guerriero S, Mascia M, Solla E, Melis GB. Laparoscopic versus abdominal myomectomy: a prospective, randomized trial to evaluate benefits in early outcome. Am J Obstet Gynecol. 1996;174:654–8.
7. Jin C, Hu Y, Chen XC, et al. Laparoscopic versus open myomectomy–a meta-analysis of randomized controlled trials. Eur J Obstet Gynecol Reprod Biol. 2009;145:14–21.
8. Sizzi O, Rossetti A, Malzoni M, et al. Italian multicenter study on complications of laparoscopic myomectomy. J Minim Invasive Gynecol. 2007; 14:453–62.
9. Garnet JD. Uterine rupture during pregnancy. An analysis of 133 patients. Obstet Gynecol. 1964;23: 898–905.

10. Parker WH, Einarsson J, Istre O, Dubuisson JB. Risk factors for uterine rupture after laparoscopic myomectomy. J Minim Invasive Gynecol. 2010;17:551–4.
11. Spong CY, Landon MB, Gilbert S, et al. Risk of uterine rupture and adverse perinatal outcome at term after cesarean delivery. Obstet Gynecol. 2007; 110:801–7.
12. Pitter MC, Gargiulo AR, Bonaventura LM, Lehman JS, Srouji SS. Pregnancy outcomes following robot-assisted myomectomy. Hum Reprod. 2013;28:99–108.
13. Liu G, Zolis L, Kung R, Melchior M, Singh S, Cook EF. The laparoscopic myomectomy: a survey of Canadian gynaecologists. J Obstet Gynaecol Can. 2010;32(2):139–48.
14. Einarsson JI, Matteson KA, Schulkin J, Chavan NR, Sangi-Haghpeykar H. Minimally invasive hysterectomies-a survey on attitudes and barriers among practicing gynecologists. J Minim Invasive Gynecol. 2010; 17(2):167–75.
15. Falcone T, Parker WH. Surgical management of leiomyomas for fertility or uterine preservation. Obstet Gynecol. 2013;121:856–68.
16. Advincula AP, Song A, Burke W, Reynolds RK. Preliminary experience with robot-assisted laparoscopic myomectomy. J Am Assoc Gynecol Laparosc. 2004;11:511–8.
17. Ascher-Walsh CJ, Capes TL. Robot-assisted laparoscopic myomectomy is an improvement over laparotomy in women with a limited number of myomas. J Minim Invasive Gynecol. 2010;17:306–10.
18. Barakat EE, Bedaiwy MA, Zimberg S, Nutter B, Nosseir M, Falcone T. Robotic-assisted, laparoscopic, and abdominal myomectomy: a comparison of surgical outcomes. Obstet Gynecol. 2011;117:256–65.
19. Bedient CE, Magrina JF, Noble BN, Kho RM. Comparison of robotic and laparoscopic myomectomy. Am J Obstet Gynecol. 2009;201:566.e1–5.
20. Gargiulo AR, Srouji SS, Missmer SA, Correia KF, Vellinga T, Einarsson JI. Robot-assisted laparoscopic myomectomy compared with standard laparoscopic myomectomy. Obstet Gynecol. 2012;120: 284–91.
21. Nezhat C, Lavie O, Hsu S, Watson J, Barnett O, Lemyre M. Robotic-assisted laparoscopic myomectomy compared with standard laparoscopic myomectomy–a retrospective matched control study. Fertil Steril. 2009;91(2):556–9.
22. Advincula AP, Xu X, Goudeau 4th S, Ransom SB. Robot-assisted laparoscopic myomectomy versus abdominal myomectomy: a comparison of short-term surgical outcomes and immediate costs. J Minim Invasive Gynecol. 2007;14:698–705.
23. Nezhat C, Nezhat F, Bess O, Nezhat CH, Mashiach R. Laparoscopically assisted myomectomy: a report of a new technique in 57 cases. Int J Fertil Menopausal Stud. 1994;39:39–44.

Vaginal Myomectomy

14

Daniel A. Tsin and Adam Magos

Introduction

Pedunculated aborting myomatas are often removed vaginally by gynecologists as an office or ambulatory procedure since the peduncle in some cases is long enough to allow the fibroids to be expelled into the vagina out of the cervix making this removal easier to perform.

These procedures vary in difficulty depending on the size, thickness and length of the peduncle. Some of the fibroids may be dislodged by simple torsion, but it is safer to tie the peduncle and then cut or coagulate it. Placing the knot in some cases could be challenging and sometimes an endo loop may be used to tie the peduncle.

However, vaginal myomectomy is much more than merely the removal of fibroids which have prolapsed into the vagina. A look at the standard surgical texts of the late nineteenth and early twentieth century shows that irrespective of their position, be they submucous, intramural or subserous, even relatively large fibroids can be removed vaginally. Our forefathers developed several techniques to make this possible, firstly to provide access (e.g. Dührssen's incision, vaginal hysterotomy, colpotomy), and then to allow debulking (e.g. "morcellement"). These procedures have all but been abandoned and forgotten, but with the current resurgence of interest in vaginal surgery, it seems timely to remind ourselves what can be achieved without laparotomy, laparoscopy or hysteroscopy.

This chapter is not meant to be a history lesson but hopefully to inspire the reader to rediscover an old art as well as discover a new one. Vaginal surgery is, after all, the domain of the gynecologist, and there is no reason why removing fibroids via the vagina should not regain its rightful place in our surgical practice.

This chapter focuses on three different types of vaginal myomectomies: the transcervical, the transvaginal and the culdopalaparoscopic approach.

Transcervical Vaginal Myomectomy (Adam Magos)

In contrast to current surgical texts of gynaecological surgery which hardly mention vaginal myomectomy, and then only in passing or for cases where a fibroid has prolapsed into the vagina, removing fibroids via the vagina used to be widely practiced by our forefathers [1]. For instance, "Gynecology and Abdominal Surgery", published in 1907 and edited by Howard A. Kelly, one of the "Big Four" founding professors at the Johns Hopkins Hospital in Baltimore, Maryland

D.A. Tsin, MD, FACOG (✉)
Department of Gynecology, Mount Sinai Hospital of Queens, Long Island City, NY, USA
e-mail: lasergyn@aol.com

A. Magos, BSc, MB BS, MD, FRCOG
University Department of Obstetrics and Gynaecology, Royal Free Hospital, London NW3 2QG, UK
e-mail: adam.magos@gmail.com

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DOI 10.1007/978-3-319-10305-1_14,

and a major figure in establishing gynaecology as a specialty in its own right, and Charles P. Noble, Clinical Professor of Gynecology at the Woman's Medical College, Philadelphia, included a whole chapter on "Vaginal myomectomy" [2]. The first paragraph makes it clear that this route of surgery was deemed suitable for the excision of fibroids irrespective of their position:

> By vaginal myomectomy is meant the removal of a fibroid tumor or tumors by the vaginal route, with the conservation of the uterus itself. The tumor may be a fibroid polyp, or it may be submucous, intramural, or subperitoneal in its location. A fibroid polyp or a submucous fibroid may be removed through the dilated cervical canal. These and the remaining types of fibroids may require anterior, bilateral, or posterior hysterotomy for their removal. Vaginal celiotomy, anterior or posterior, may be necessary for the removal of subperitoneal fibroids.

This chapter also contained a brief but useful history of the procedure, and mentioned pioneers such as Jean Zuléma Amussat (Paris, France), Washington Atlee (Pennsylvania, USA), Thomas Addis Emmet (New York, USA), Theodore Gaillard Thomas (New York, USA), Jules-Émile Péan (Paris, France), Eugène-Louis Doyen (Paris, France) and Johann Veit (Leiden, Germany). It is evident that by the end of the nineteenth century, the use of hysterotomy, traction and morcellation had been perfected, and special instruments to facilitate the procedure developed such as the spoon saw, enucleators and the écraseur chain (Figs. 14.1, 14.2, and 14.3) [3].

While there were a wide range of indications for vaginal myomectomy, fibroids which were over-large, which Noble who wrote the chapter defined as "several pounds", and "lack of room in the vagina" were considered to be relative contra-indications, although incising the perineum was an option in cases of the latter. However, one cannot but get the impression that relatively large fibroids were being removed vaginally as well demonstrated by a case report published in the British Medical Journal in 1893. Dr. James Murphy, then President of the North of England Branch of the British Medical Association, described a patient with a myomatous uterus extending up to the umbilicus who underwent a successful vaginal myomectomy using the technique of "morcellement" popularized by Jules-Émile Péan (Fig. 14.4) [4].

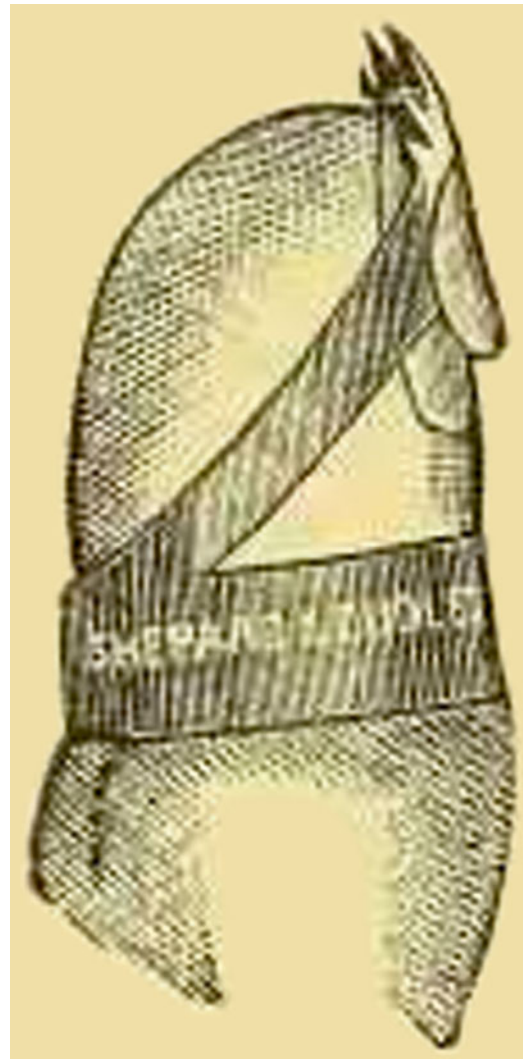

Fig. 14.1 Emmet's enucleator which can be used to dissect around the fibroid (Taken from Ref. [3])

Another surgical textbook, "Operative Gynecology" written by Harry Sturgeon Crossen (USA) and published in 1917, is worthy of study as it included beautiful illustrations of the various different types of vaginal myomectomy, some of which I have included for demonstration purposes later in this chapter [5]. Many of these classic books are available for download for free from www.archives.org, a website well worth a visit.

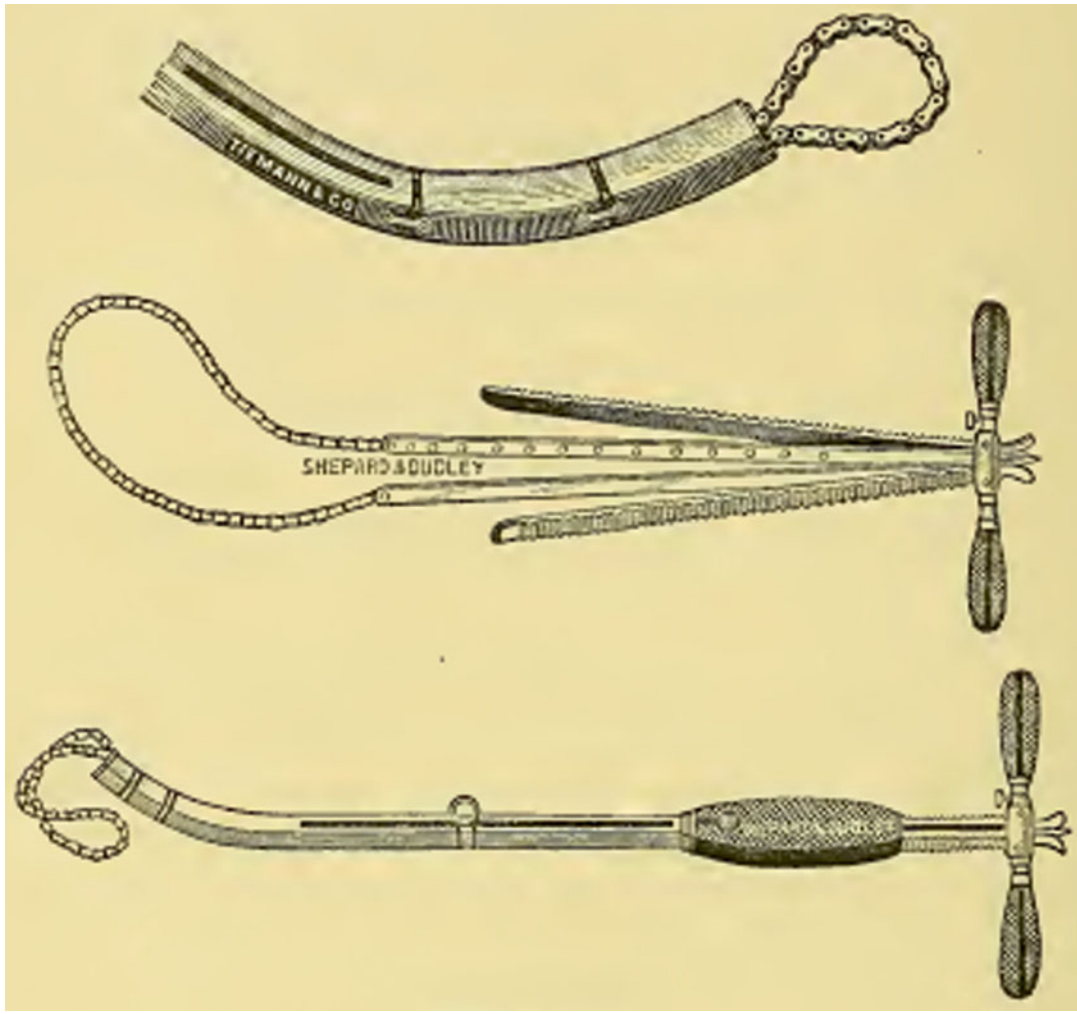

Fig. 14.2 Emmet's écraseur chain which is placed around a fibroid polyp to lacerate and crush the tissue and facilitate the application of a suture (Taken from Ref. [2])

Classification of Vaginal Myomectomy

As the term vaginal myomectomy relates to several different procedures, we have found it useful to classify the various types of vaginal myomectomies, and now use the system summarized in Table 14.1 [6].

There are basically four approaches which can be used depending on the position and size of the fibroid or fibroids. Prolapsed submucous fibroids are ideally removed through the cervix (Type 1 procedure). Cervical dilatation or a cervical/uterine incision (Types 2 and 3a/b procedures respectively) can be used to access fibroids higher in the uterus, whether they are intracavitary, submucous or intramural. Intramural fibroids can also be approached via an anterior or posterior colpotomy, and this is the route of choice for those which are subserous (Type 4 procedure).

Type 1 Vaginal Myomectomy

The avulsion of a submucous (or cervical) fibroid which has prolapsed into the vagina is the simplest and at the same time the original vaginal myomectomy as described by the early pioneers such as Ammusat and Atlee. In contrast to the other types of vaginal myomectomy, this is the

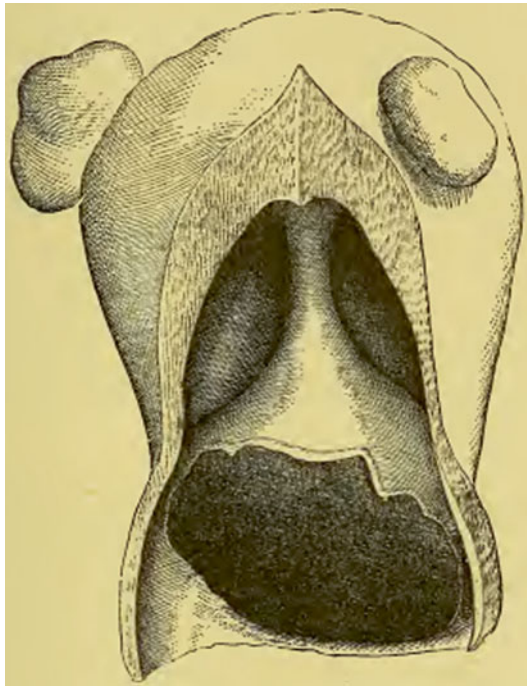

Fig. 14.3 Pedunculated intracavitary fibroid, partially removed by the écraseur (Taken from Ref. [3])

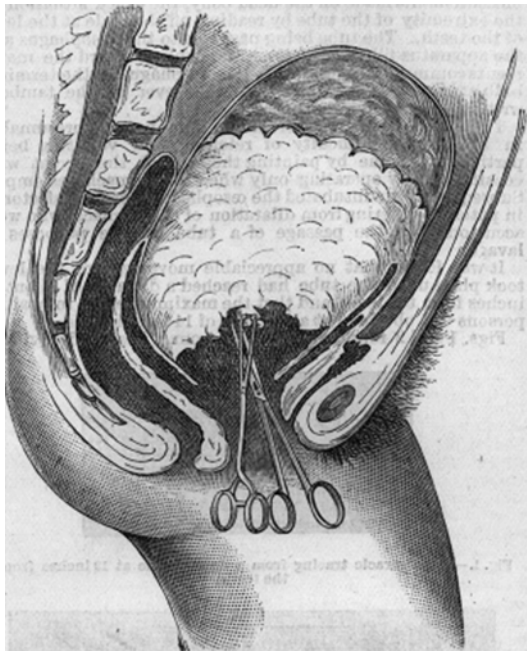

Fig. 14.4 Vaginal myomectomy "par morcellement" (Taken from Ref. [4] With permission from BMJ Publishing Group Ltd)

Table 14.1 Classification of vaginal myomectomy

Type	Description
1	Avulsion of prolapsed pedunculated submucous fibroid
2	Non-incisional access to intracervical or intracavitary fibroids
3a	Dührssen cervical incision to access to intracavitary/submucous/intramural fibroids
3b	Hysterotomy to access to intracavitary/submucous/intramural fibroids
4	Anterior or posterior colpotomy to access to intramural and subserous fibroids

Modified from Ref. [6]

technique which historically has not been abandoned as is evident from published series as well as textbooks of today [7–10]. Such patients typically present with heavy, unscheduled vaginal bleeding, and examination confirms a mass in the upper vagina. The excision of a prolapsed fibroid in the vagina has also been reported after pregnancy, the typical scenario being of a major postpartum haemorrhage which is resistant to uterotonic drugs [11, 12] (Fig. 14.5).

Depending on the size and vascularity, the fibroid can be excised by twisting its pedicle or following clamping, cutting and suturing the base. Whichever technique is used, we routinely carry out a hysteroscopy afterwards to check that the fibroid has been completely removed; if not, any residual fibroid tissue in the uterine cavity can be resected. If the cervical canal is too dilated to allow sufficient uterine distension, we place a couple vulsellums on the cervix or even perform a temporary cervical cerclage to narrow the cervix and reduce the leakage of uterine irrigant.

Type 2 Vaginal Myomectomy

If a fibroid is in the cervical canal or in the lower uterine cavity, it may be possible to remove it vaginally without cutting the cervix. In the non-pregnant uterus, cervical dilatation with conventional mechanical dilators or preparation with laminaria tents (Laminaria japonica) may be required to allow sufficient access prior to avulsion or morcellation in the case of larger fibroids, as, for instance, described by Milton Goldrath [13, 14]. However, unless the fibroid is small, our preference

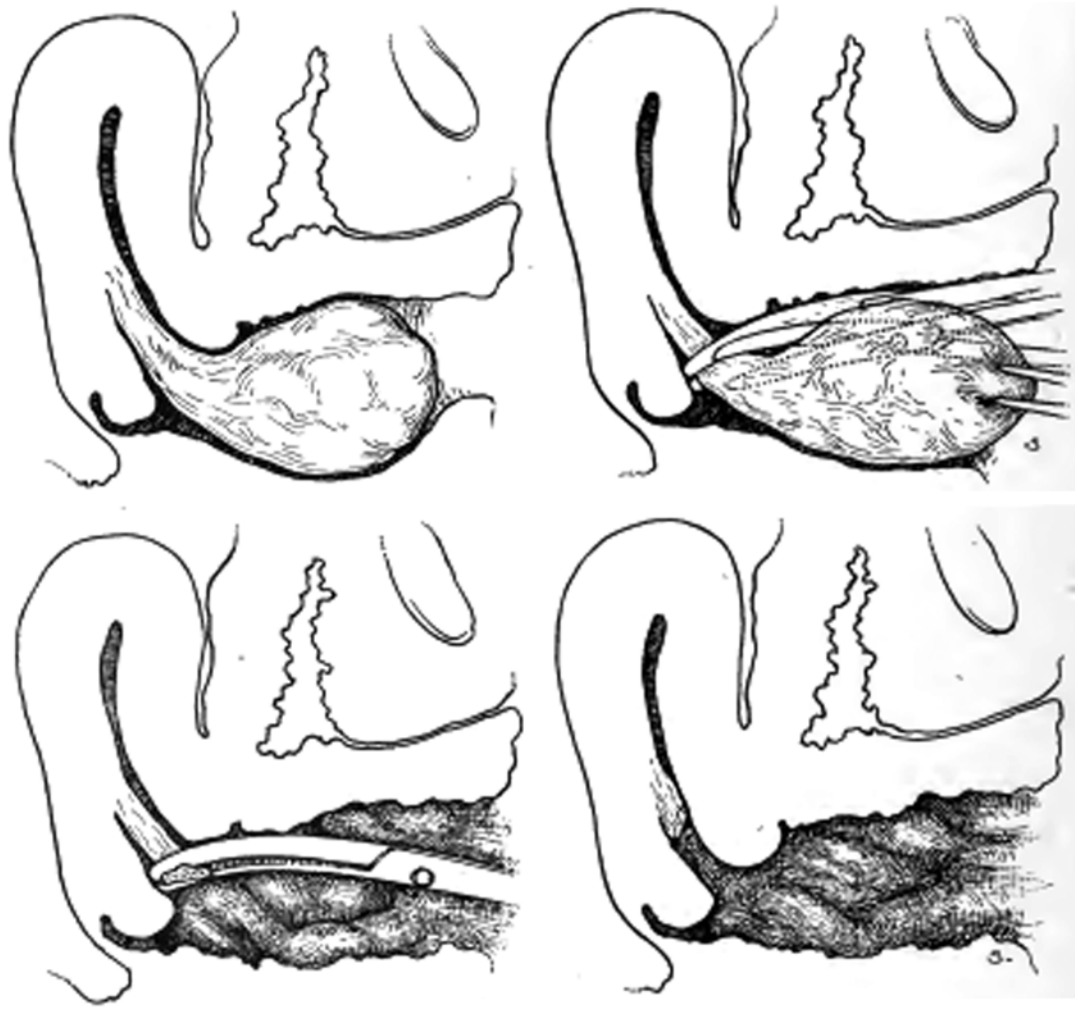

Fig. 14.5 Vaginal myomectomy for pedunculated fibroid in the vagina (Taken from Ref. [5])

is to carry out a Type 3 procedure and cut the cervix using a Dührssen's incision in such cases, as described in the next section, as in our view this affords better access to the uterine cavity.

The situation may well be different after pregnancy. Martindale et al. described a case of secondary postpartum haemorrhage which was managed by the vaginal removal of an 8 cm submucous fibroid without cutting the cervix [15].

Type 3a Vaginal Myomectomy

Alfred Dührssen (1862–1933) was a prominent figure in German gynaecology, and the cervical incisions which bear his name, typically consisting of 3–4 cervical incisions extending up to the vagina, were originally used to allow immediate vaginal delivery of the fetus before full dilatation [16]. Dührssen's incision was adapted for the performance of vaginal myomectomy in the nineteenth century as it facilitated access to fibroids which would otherwise be inaccessible and made the removal of relatively large intracavitary fibroids possible with the aid of morcellation. As an example of the technique, Fig. 14.6 is taken from "Gynecological operations, including non-operative treatment and minor gynecology" by Henri Hartmann published in 1913 [17].

We prefer to make a posterior rather than anterior cervical incision as this avoids any risk of bladder injury, but if we suspect that the incision may have to be extended into the uterine body as a hysterotomy, we start with an anterior Dührssen's incision as in our experience it is easier to repair an anterior hysterotomy than a posterior one. Either way, once the cervix has been cut, the fibroid is grasped with strong forceps such as a vulsellum or Lane's tissue forceps and enucleated with or without morcellation. Following the myomectomy, the cervical incision is repaired (Fig. 14.7).

Fig. 14.6 Vaginal myomectomy done with the help of a posterior Dührssen's incision (Taken from Ref. [17])

At our institution, a type 3a vaginal myomectomy is considered an alternative to hysteroscopic myomectomy in women with larger type 0 or 1 submucuous fibroids sited in the lower uterine cavity. With fibroids >5 cm in diameter, most gynaecologists are reluctant to offer hysteroscopic surgery, but as demonstrated above, there is no reason why myomectomy cannot be done vaginally using this technique combined with morcellation. In fact, in our view, the procedure should be considered even if the fibroid is smaller. For instance, the hysteroscopic resection of a 4 cm fibroid is time consuming, and with longer operating times comes the risk of fluid overload. Vaginal myomectomy in such cases is not only much quicker, but fluid overload is impossible.

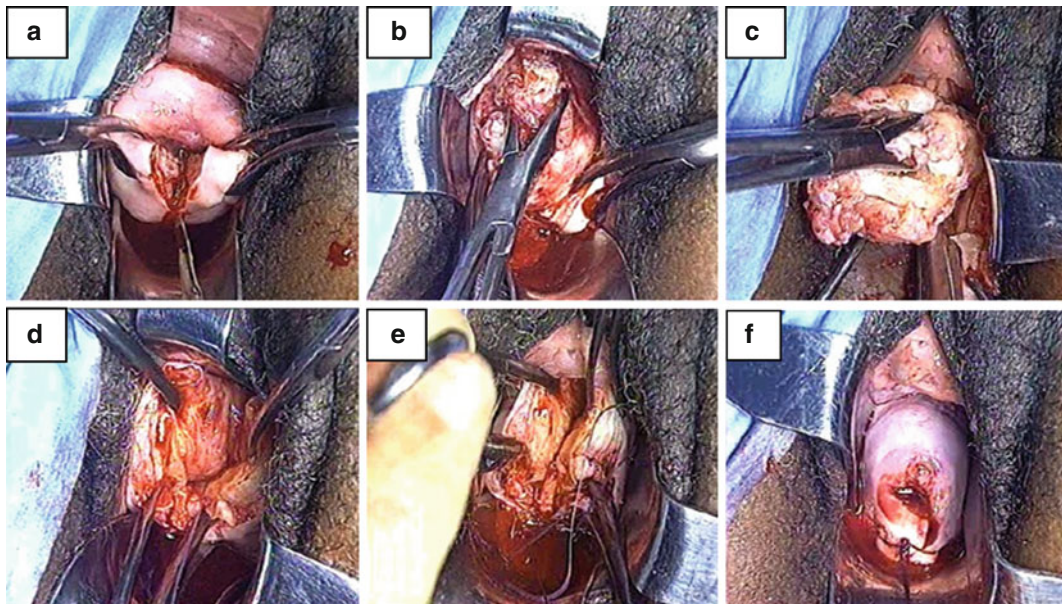

Fig. 14.7 Excision of a large submucous fibroid with the aid of a Dührssen's incision and morcellation. (**a**) A osterior Duhrssen's incision is made. (**b**) The fibroid is grasped with tissue forceps. (**c**) The fibroid is avulsed. (**d**) Appearance of the cervical incision after removal of the fibroid. (**e**) The cervical incision is sutured. (**f**) The appearance of the cervix on completion of th surgery

Type 3b Vaginal Myomectomy

It is, however, extension of the cervical incision into a hysterotomy which, above all, increased the versatility and indications for vaginal myomectomy. Fibroids which are intramural or sited in the upper uterine cavity, and which are seemingly out of range for the vaginal surgeon even if the cervix is cut become a realistic target following a hysterotomy. As demonstration of this, Fig. 14.8 is taken from "Operative Gynecology" published in 1917.

If an anterior hysterotomy is used, which is our preference, the bladder invariably has to be dissected away from the cervix and anterior uterine wall to protect it from injury. To do this, we make an anterior semi-circular transverse incision at the cervico-vaginal junction and dissect the bladder upwards before incising the cervix and uterine body anteriorly in the midline. Occasionally, this results in an anterior colpotomy being made, but that is of no consequence.

A type 3b vaginal myomectomy is suitable for excising large intracavitary, submucous or intramural fibroids (Fig. 14.9). In such a case, morcellation allows the fibroids to be debulked piecemeal, and various morcellation techniques have been described as shown from this series of drawings taken from "Gynecological operations, including non-operative treatment and minor gynecology" published in 1913 (Fig. 14.10).

Irrespective of the size of fibroid, dissection of the pseudocapsule is done with fingers or Mayo scissors while exerting downward traction on the fibroid. As already mentioned, we use vulsellums or Lane's tissue forceps for this, but a myoma screw can also be inserted into the fibroid as demonstrated in Fig. 14.6. The larger the fibroid, the greater care has to be taken to avoid accidental perforation of the uterus and damage to surrounding structures from sharp instruments during morcellation. It is best to take relatively small bites initially and always to cut towards the centre of the fibroid.

Apart from the avoidance of any abdominal incisions, the beauty of this approach to myomectomy, compared with laparoscopic myomectomy for instance, is that the uterus can be repaired much more quickly using conventional instruments and sutures. There is generally surprisingly little bleeding during the surgery, perhaps because traction on the uterus results in kinking of the uterine vessels; we never use vasoconstrictors or other uterotonic agents.

Transvaginal Vaginal Myomectomy via Colpotomy (Adam Magos)

Fibroids which are subserous are not suitable for transcervical myomectomy. In such cases, vaginal myomectomy via an anterior or posterior colpotomy, that is a type 4 vaginal myomectomy, can be considered. Just as the other techniques, this approach was included in textbooks of the late nineteenth and early twentieth century but seemingly abandoned until the 1994 when our Unit reported on 32 out of 35 women managed successfully by transvaginal myomectomy [18]. Since then, there has been a world-wide resurgence of interest in this technique for removing subserous as well as intramural fibroids as evidenced by numerous scientific publications, including not only descriptive series but randomized trials and meta-analyses [19–35]. Although the data is limited, vaginal myomectomy comes out favourably compared with laparoscopic myomectomy.

We prefer to operate via posterior colpotomy as this avoids the need for bladder dissection and also means that the surgery takes place in the relatively larger pelvic basin rather than under the pubic arch. For this reason, if the dominant fibroid is posterior or fundal, we start with a posterior colpotomy, and only if the largest fibroid is anterior do we commence with an anterior colpotomy. On rare occasions, both posterior and anterior colpotomies have to be made (Fig. 14.11).

Having made the colpotomy and entered the peritoneal cavity, the fibroid has to be maneuvered into the incision. This can be technically the most difficult part of the procedure. Hooks, tissue forceps or vulsellums risk tearing the uterus, so our preference is to use a single suture to "walk up" the uterine wall towards the fundus until the fibroid is reached (Fig. 14.12).

Depending on the size of the uterus and fibroid(s), it may be possible to pull the uterus through the colpotomy into the vagina, but more often than not, this is not possible, and the

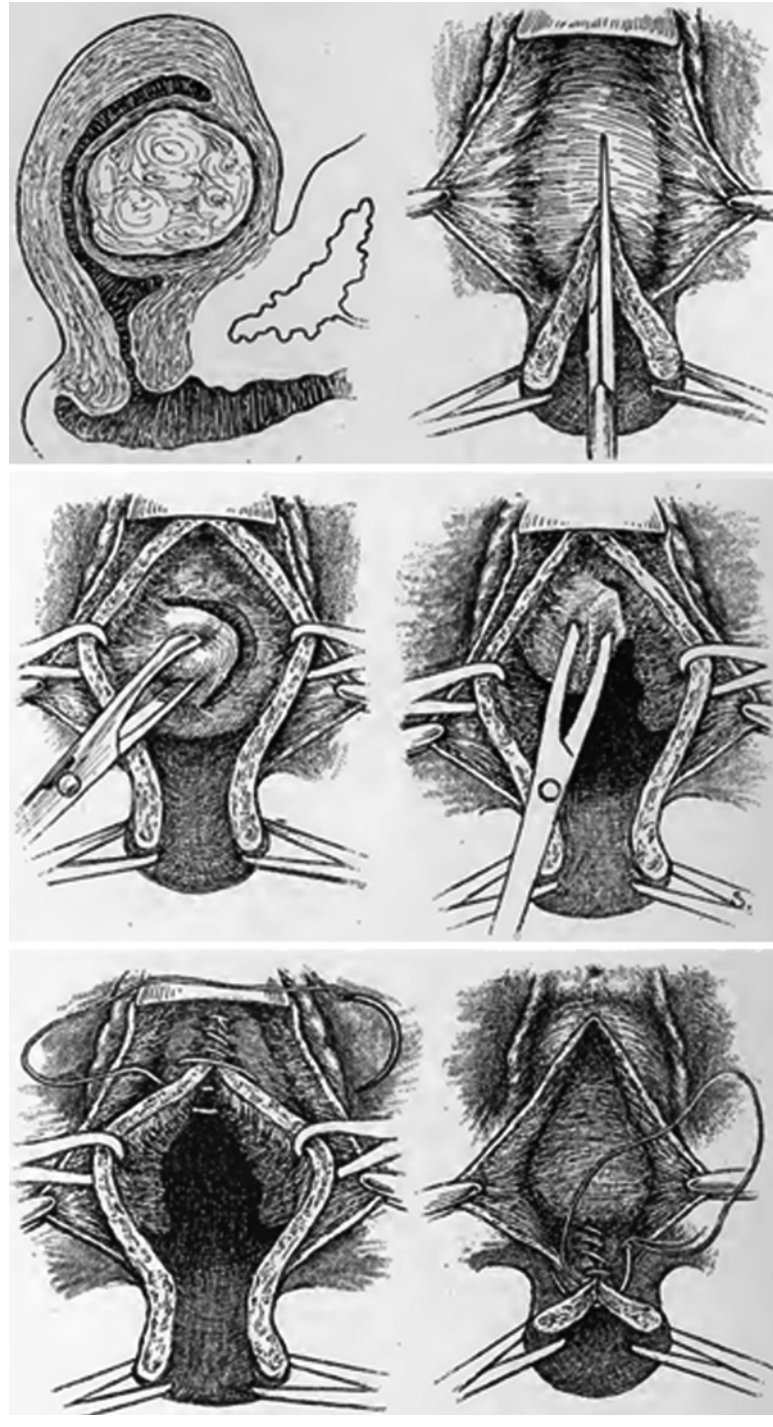

Fig. 14.8 Removal a submucous fibroid after making an anterior hysterotomy (Taken from Ref. [5])

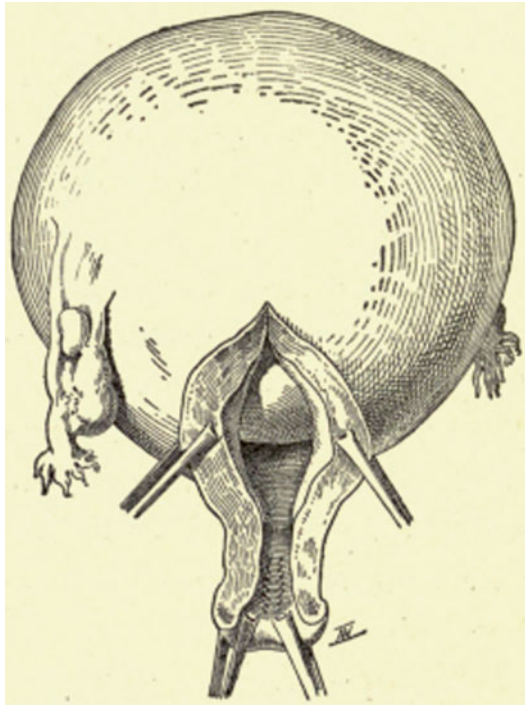

Fig. 14.9 Anterior hysterotomy to gain access to a large intracavitary fibroid (Taken from Ref. [17])

myomectomy has to be done through the colpotomy incision. We steady the uterus by placing tissue forceps or sutures into the uterine serosa on either side of a vertical incision over the fibroid (Fig. 14.13). Depending on the size of the fibroid, it is excised with or without morcellation (Figs. 14.14 and 14.15).

The procedure is repeated in the case of multiple fibroids until eventually the uterus has been so debulked that it can be pulled into the vagina. Uterine repair, therefore, is done in the vagina and not the pelvis which greatly facilitates this stage of the surgery. Conventional instruments and sutures are of course used, and as previously mentioned, we consider this to be a great advantage over laparoscopic myomectomy (Fig. 14.16).

Before replacing the uterus into the pelvis, a careful check should be made for haemostasis. Just as with the other techniques of vaginal myomectomy, intra-operative bleeding does not tend to be a problem with a type 4 procedure, but once the uterus is repositioned, traction released and the uterine vessels unkinked, oozing from the uterine incision(s) becomes a potential problem.

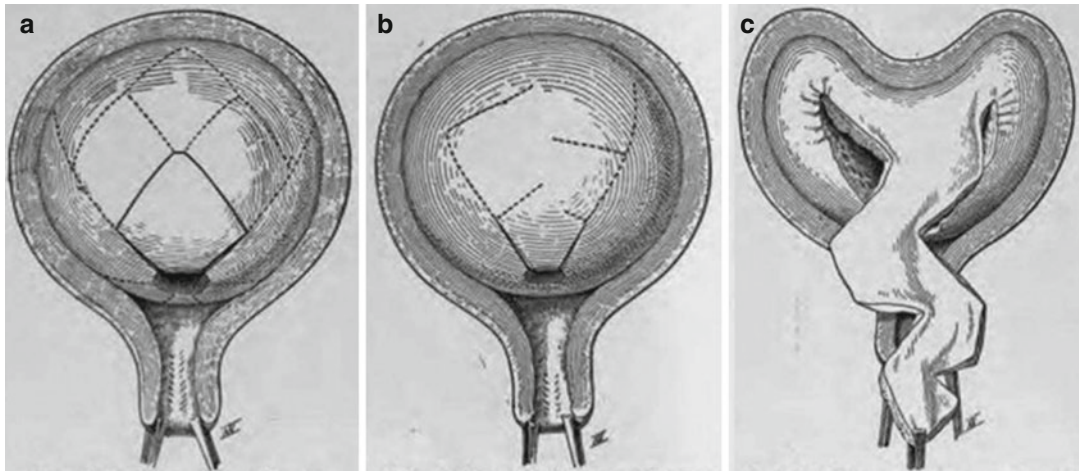

Fig. 14.10 Two types of morcellation techniques, (**a**) lozenge, (**b**) Echelle or ladder, (**c**) result of Echelle morcellation (Taken from Ref. [17])

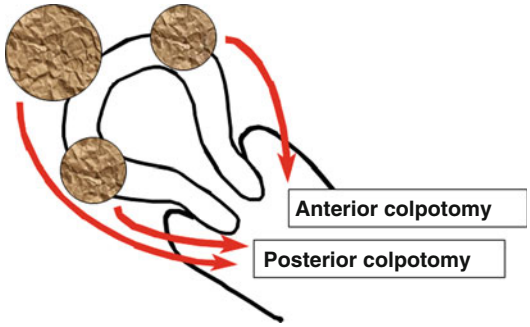

Fig. 14.11 Posterior or anterior colpotomy is made depending on the site of the dominant fibroid

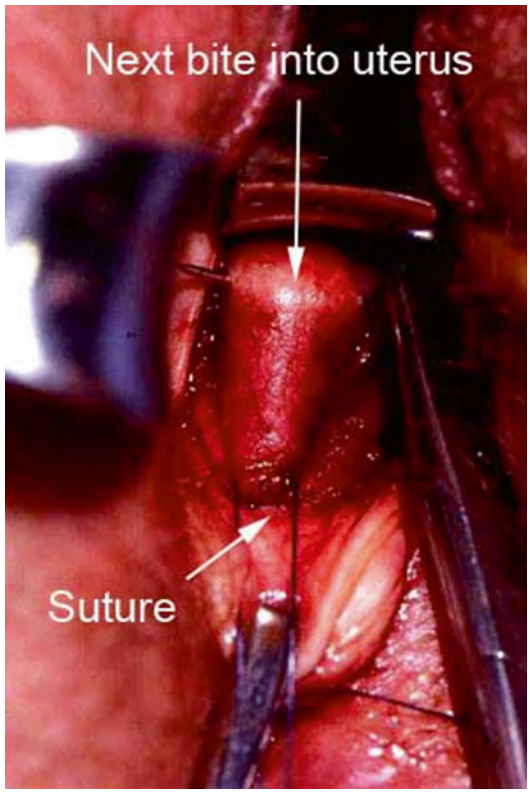

Fig. 14.12 The "walking up" technique to maneuvere the uterus into the colpotomy incision

If there any uncertainty, there is no reason why a drain cannot be inserted into the pelvis for the first 24 h or so before closing the colpotomy incision (Fig. 14.17).

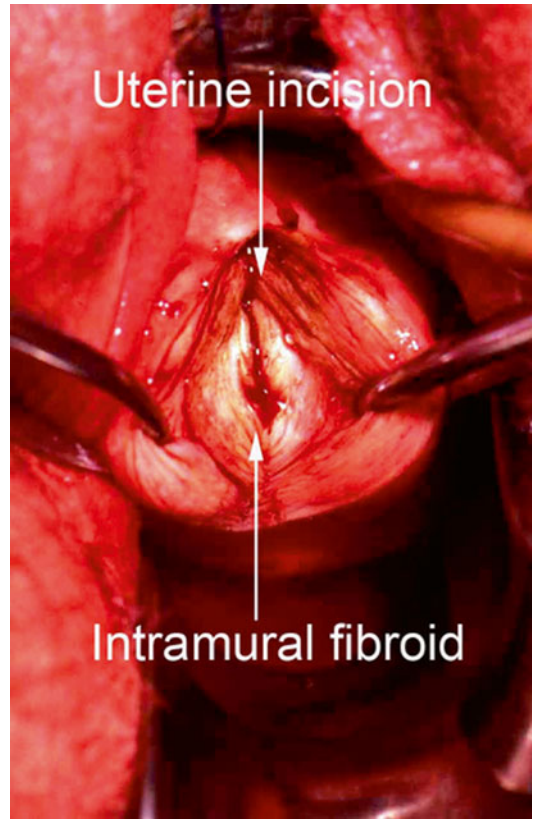

Fig. 14.13 The uterus is held and a vertical incision made into the uterine serosa and overlying myometrium to gain access to the fibroid

Key to the success of vaginal myomectomy, as with all surgery, is careful patient selection. The three pre-requisites are good uterine mobility, good vaginal access, which really means normal mobility and access, and a uterus which is not over-large. We would be reluctant to attempt a type 4 procedure if the uterus is greater than the equivalent of 14 weeks gestation. The position of the dominant fibroid is also important, a posterior fibroid being the ideal case. Conversely, a fundal fibroid might be better managed by laparoscopy. If a vaginal myomectomy fails needing conversion to laparotomy, it is likely to be related to poor patient selection. Morbidity, otherwise, compares favourably with other routes of myomectomy [28, 36]. All our patients are treated with a broad spectrum prophylactic antibiotic during and for 5 days after surgery.

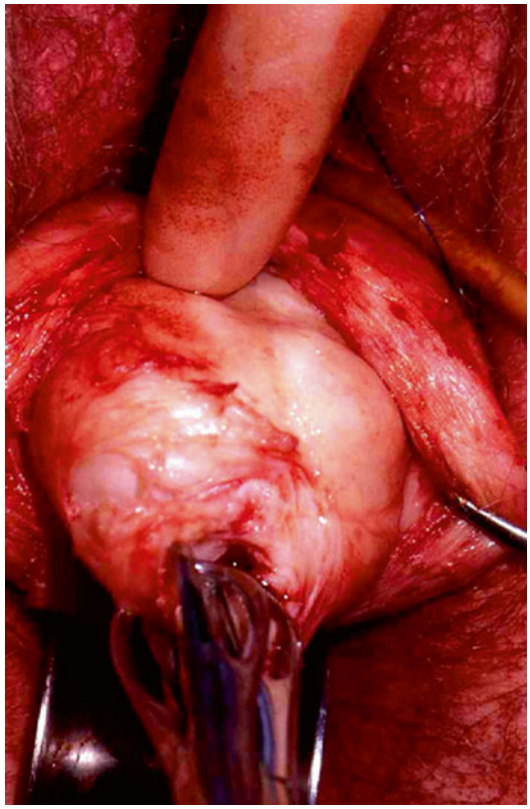

Fig. 14.14 A relatively small fibroid is being excised by traction and sharp or blunt dissection

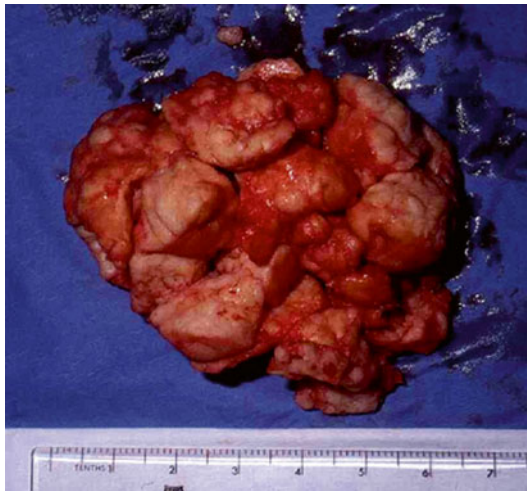

Fig. 14.15 A large posterior fibroid which was removed by morcellation via a posterior colpotomy

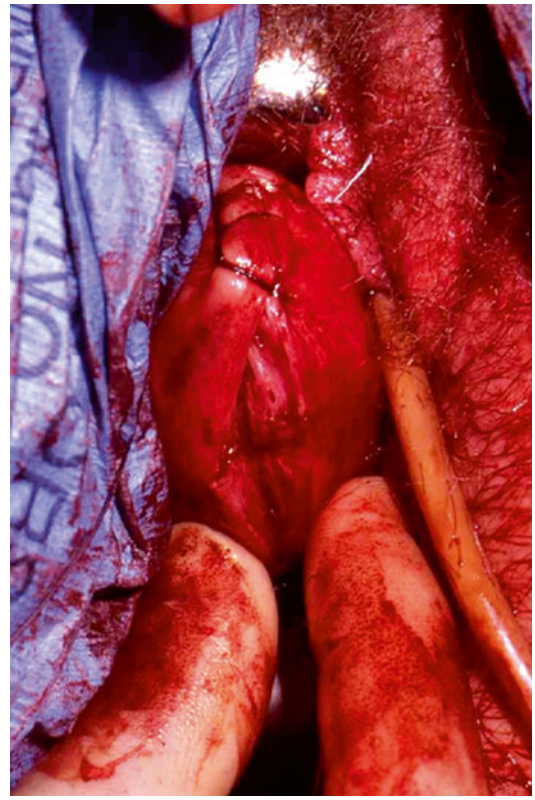

Fig. 14.16 Closing the uterine incision in a type 4 vaginal myomectomy

Culdolaparoscopy Myomectomy

The concept of natural orifice transluminal endoscopic surgery (NOTES) is a big contribution to a minimally invasive approach for some general surgeries, gynecological and urology procedures. This is a revolutionary approach that focuses on transgastric peritoneoscopy [37] but also includes a transvaginal endoscopic surgery for performing some of the above mentioned procedures while leaving no visible scars in the abdomen. These works are associated with innovations in flexible technology, magnets, secured independent tools, percutaneous needles, double anchor suspension systems and robotics. Transvaginal surgery via colpotomy is a well-known gynecological approach, which consists of making an incision in the posterior cul-de-sac to operate and extract

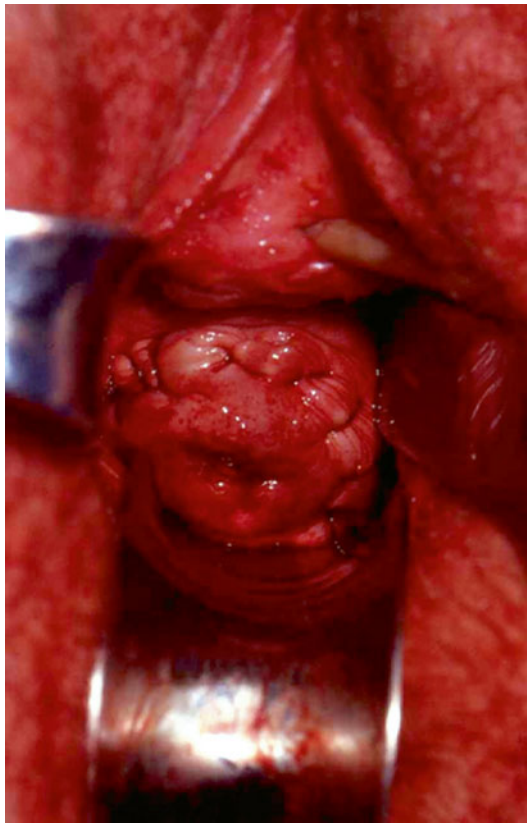

Fig. 14.17 The appearance of the cervix and vagina following repair of an anterior colpotomy

specimens via the vaginal route. Colpotomy is used during laparoscopy for specimen extraction, avoiding additional abdominal scars [38, 39].

Historical Background of Culdolaparoscopic Myomectomy

Professor Von Ott described transvaginal endoscopy first under the name of Ventroscopy during a meeting at The Society of Gynecology and Obstetrics of San Petersburg (Russia) in 1901. Dr. Ott used colpotomy, placing the patient in the Trendelenburg position, while placing a tube thorough the vagina inside the pelvic cavity and illuminating the pelvis and abdomen [40].

A few years later several optical instruments related to cystoscopy began to be used for visualization of the thorax and abdomen. Additionally, the pelvis was explored via a vaginal route. Dr. Emanuel Klaften presented at a meeting of the Vienna Medical Society (Austria) a technique of Colpolaparoscopy in 1937. Dr. Klaften designed an optical instrument with a light and a 90° angle vision. Several diagnostic procedures and few limited surgeries were performed using this technique [41].

Dr. A. Decker and T. Cherry described transvaginal endoscopy in the knee chest posture under the name of Culdoscopy in 1944.

The operations were done first at the Knickerbocker Hospital in New York, New York (USA) (Fig. 14.18).

Culdoscopy was used for transvaginal endoscopy for more than 25 years in thousands of cases worldwide. It was used with local or general anesthesia. Patients received prophylactic antibiotics and antiseptic vaginal preparations. Complications were rare, mostly associated with extra peritoneal rectal perforation that required prolonged antibiotic treatment [42].

During the 1960s, gynecologist began using laparoscopy, which offered a better visual field than culdoscopy. Laparoscopy is more traumatic than culdoscopy but offered the advantage to explore the pelvis and the abdomen, and to use additional ports. Culdoscopy was abandoned for three decades. Meanwhile, laparoscopy benefited from the advances of new technology, such as optic fibers, video, hundreds of instruments, lasers, flexible technology and robots. A revival of transvaginal endoscopy happened thanks to the technological advances and the independent works on transvaginal hydrolaparoscopy [43], fertiloscopy and culdolaparoscopy circa 1998.

Transvaginal Hydrolaparoscopy/Fertiloscopy is an ambulatory or office procedure, done with local anesthesia. Flexible endoscopy was also used in culdoscopy. It could be used instead of laparoscopy. The advantage of the flexible instruments over the rigid instruments is the ability to change the visual angle up to 180°, allowing to visualize the pouch of Douglas, the anterior face of the uterus and the broad ligaments all of them blind spots for the rigid culdoscopy.

Fig. 14.18 Decker Culdoscope in its original case courtesy of www.culdoscopy.com

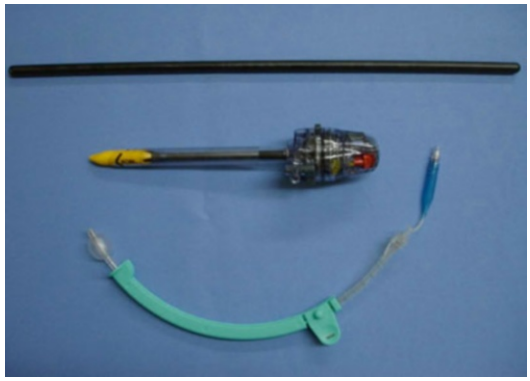

Fig. 14.19 Uterine manipulator trocar and rood

Culdolaparoscopy

Culdolaparoscopy is a hybrid procedure for the pelvis and that goes beyond the pelvis into the abdominal cavity combining operative culdoscopy, a natural orifice surgery with laparoscopy and minilaparoscopy. This is an easy procedure for the experienced laparoscopist [44].

The patient selection is done like in laparoscopy, the patient must also have easy access to the posterior vaginal fornix and no obliteration of the posterior cul-de-sac. The patient receives prophylactic antibiotics and a bowel preparation. The operating room setup consists of two mobile monitors that serve the surgeon and the assistant. The surgeon could move from a lateral position to operate between the patient's legs. The patient is placed in a modified dorsolitotomy position and in Allen type of telescopic stirrups. The vagina is cleansed with antiseptic and a Foley catheter and a uterine manipulator are placed inside the bladder and the uterus. The procedure is done with laparoscopy instruments no larger than 5 mm in diameter preferably near 3 mm. The vaginal port consists of a 10 mm diameter by 46 cm in length plastic rod (Port-Saver TM manufactured by ConMed) mounted in a 12 mm diameter 15 cm length insufflation cannula. The vaginal port is placed under laparoscopic or minilaparoscopic surveillance. The uterus is pushed with the uterine manipulator anterior and cephalic exposing the pouch of Douglas (Fig. 14.19). The rod is placed against the posterior vaginal fornix, and the end of the rod is seen as a protrusion in the center of the cul-de-sac. An incision is done at the tip of the protrusion with a minilaparoscopic spatula or hook (Fig. 14.20).

Then with gentle yet steady pressure the rod is introduced into the Pouch of Douglas and the cannula is slid over. The vaginal port could be also placed with a sharp trocar, this is not as safe as the blunt trocar entry described above. A meticulous technique is essential. Whenever this

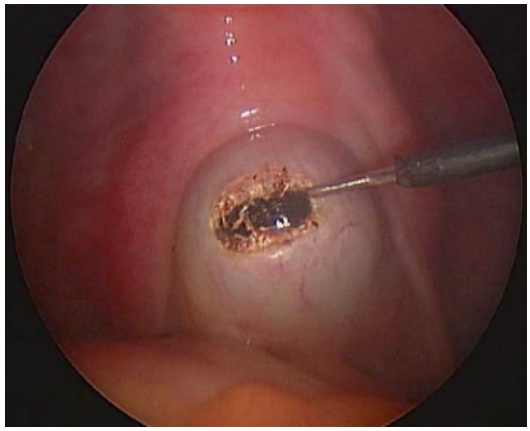

Fig. 14.20 Incision in the cul-de-sac

approach is used a major concern is bowel perforation. The protruding point must be clearly identified in position in the middle of the pouch of Douglas. The insertion needs to be precise. Attention should be kept to avoid lateral movements since the trocar has a tendency to slide laterally under pressure. I advise not to attempt to use this armed sharp trocar entry till enough experience is gathered with a blunt trocar entrance.

When in place, the vaginal port fits tight and is well sealed. At this time, the insufflation line is attached to the vaginal port. The patient's thighs were brought to about 15° above the horizontal position while keeping the knees flexed. The pnemoperitoneum is not lost the port is multifunctional it could be used for insufflation, visualization, operation and extraction. The vaginal port could be used to place laparoscopes, gastroscopes, sutures, laparoscopy reins, secured independent tools, magnets and experimental micro robotics as well as larger or longer instruments, like clip appliers, endoscopic gastrointestinal anastomosis clamps, morcellators, large bipolar clamps, irrigators and it allows for extraction of large specimens.

Most of the myomectomies are done with infiltration 1 in 200 dilution of vasopressin, Using 3 mm abdominal instruments. the vaginal port is used for insufflation, could aid in the exposure, 10 mm plastic rod facilitated the exposures since 3 mm instruments are more delicate and with little strength to mobilized sizable uterine myomatas. The fibroid is usually enucleated and a 10 mm tenaculum is used to hold and extract the specimen, Fibromas as large as 8 cm could be removed in most cases. For large fibroids extraction the culdolaparoscopy options are colpotomy extension or transvaginal intra abdominal morcellation. For the colpotomy extension we placed the posterior fornix under lateral and caudal tension obtained by lateral and downward pulling the vaginal cannula in order to make the fornix wall thinner and then cutting for a transverse extension using the cannula as a backstop one site at a time.

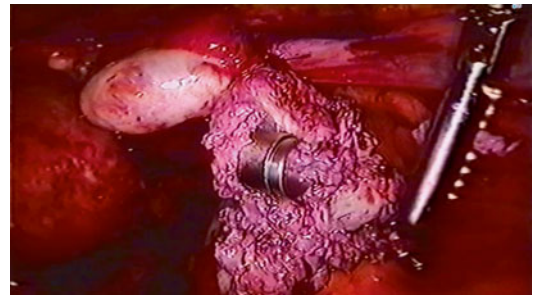

Fig. 14.21 Motorized morcellation via a vaginal port

The intra abdominal morcellation is performed with a reusable motorized morcellator placed via the vaginal port. The laparoscopic surveillance is done via an abdominal port, while the operation is done from the vaginal port (Fig. 14.21). The operation utilizes a motorized blade in the opposite direction of the optics requires good communication, orientation and coordination among members of an experienced team. Transvaginal use of disposable motorized morcellator inserted without a cannula needs a dedicated 3 mm abdominal port only for high flow insufflation to keep the pneumoperitoneum. The closure of the colpotomy is done vaginally using chromic sutures [45, 46]. Gynecologists occasionally use colpotomy to remove large specimens, surgeons rarely use vaginal extraction for the removal of the appendix, gallbladder, spleen, tumor of the stomach or the large bowel and urologist rarely remove the kidney via colpotomy. In many cases they were frustrated with the loss of pneumoperitoneum. Culdolaparoscopy,

which uses a sealed vaginal port, avoids the problem of losing the pneumoperitoneum since instruments could be easily introduced via the vaginal port for extraction, and when needed the pneumoperitoneum reinstated [47].

Even after the vaginal port is removed completely it is very easy to place the vaginal port back and reestablish the pneumoperitoneum in most cases using the vaginal port for insufflation. Whit culdolaparoscopy the vaginal port function as an entrance as well as an exit port and all ports abdominal or vaginal are multifunctional.

The surgeon is able to use and change the function of any port according to the requirement or stage of the procedure and overcome what up till now are considered limitations for minilaparoscopy or operative culdoscopy. Published experiences in transvaginal NOTES and our experience in culdolaparoscopy appears to reduce morbidity, pain and the risk of port site hernias [48].

References

1. Breech LL, Rock JA. Leiomyomata uteri and myomectomy. In: Rock JA, Jones HW, editors. Te Linde's operative gynecology. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
2. Noble CP. Vaginal myomectomy. In: Kelly AH, Noble CP, editors. Gynecology and abdominal surgery. Philadelphia: W.B. Saunders Company; 1907. p. 713–7.
3. Emmet TA. The principles and practice of gynaecology. 2nd ed. New York: Henry C Lea; 1880.
4. Murphy J. Notes of a case of vaginal myomectomy par morcellement. Br Med J. 1893;1(1676):285.
5. Crossen HS. Operative gynecology. St. Louis: C.V. Mosby Company; 1917. p. 277–83.
6. Thomas B, Magos A. Subtotal hysterectomy and myomectomy – vaginally. Best Pract Res Clin Obstet Gynaecol. 2011;25:133–52.
7. Brooks G, Stage AH. The surgical management of prolapsed pedunculated submucous leiomyomas. Surg Gynecol Obstet. 1975;141:397–8.
8. Riley P. Treatment of prolapsed submucous fibroids. S Afr Med J. 1982;63:22–4.
9. Ben Baruch G, Schiff E, Menashe Y, et al. Immediate and late outcome of vaginal myomectomy for prolapsed pedunculated submucous myoma. Obstet Gynecol. 1988;72:858–61.
10. Golan A, Zachalka N, Lurie S, et al. Vaginal removal of prolapsed pedunculated submucous myoma: a short, simple, and definitive procedure with minimal morbidity. Arch Gynecol Obstet. 2005;271:11–3.
11. Salamalekis E, Loghis C, Panayotopoulos N, et al. Vaginal myomectomy in the treatment of postpartum haemorrhage. J Gynecol Surg. 1996;12:275–7.
12. Heisler CA, LaGrand JP, McSpadden F. Vaginal removal of a partially expelled massive leiomyomata (sic.) in a postpartum patient after cesarean delivery: a case report. J Pelvic Med Surg. 2007;13:213–5.
13. Goldrath MH. Vaginal removal of the pedunculated submucous myoma: the use of laminaria. Obstet Gynecol. 1987;70:670–2.
14. Goldrath MH. Vaginal removal of the pedunculated submucous myoma. J Reprod Med. 1990;35:921–4.
15. Martindale EA, Subris JF, Wake CR. Severe secondary postpartum haemorrhage successfully managed by vaginal myomectomy. J Obstet Gynaecol. 1998;18:380–1.
16. Mayes HW. Dührssen's incisions. Am J Surg. 1951; 81:303–6.
17. Hartmann H. Gynecological operations, including non-operative treatment and minor gynecology. Philadelphia: P. Blackiston's Son & Co; 1913.
18. Magos AL, Bournas N, Sinha R, et al. Vaginal myomectomy. Br J Obstet Gynaecol. 1994;101:1092–4.
19. Bessenay F, Cravello L, Roger V, et al. Vaginal myomectomy. Contracept Fertil Sex. 1998;26:448–51.
20. Davies A, Hart R, Magos AL. The excision of uterine fibroids by vaginal myomectomy: a prospective study. Fertil Steril. 1999;71:961–4.
21. Birsan A, Deval B, Detchev R, et al. Vaginal and laparoscopic myomectomy for large posterior myomas: results of a pilot study. Eur J Obstet Gynecol Reprod Biol. 2003;110:89–93.
22. Agostini A, Deval B, Birsan A. Vaginal myomectomy using posterior colpotomy: feasibility in normal practice. Eur J Obstet Gynecol Reprod Biol. 2004;116: 217–20.
23. Wittich AC. Vaginal myomectomy through an anterior colpotomy. J Pelvic Med Surg. 2005;11:145–7.
24. Zhang J, Huang L, Chen YH, et al. Clinical analysis of 45 cases of vaginal myomectomy. Zhonghua Fu Chan Ke Za Zhi. 2005;40:659–61.
25. Carminati R, Ragusa A, Giannice R, Pantano F. Anterior and posterior vaginal myomectomy: a new surgical technique. MedGenMed. 2006;8:42.
26. Wei F-H, Zhao X-D, Zhang Y. Feasibility and safety of vaginal myomectomy: analysis of 90 cases. Chin Med J. 2006;119:1790–3.
27. Rovio PH, Pentti AE, Heinonen K. Transvaginal myomectomy with screw traction by colpotomy. Arch Gynecol Obstet. 2006;273:211–5.
28. Agostini A, Gerbeau S, Al Nakid M, et al. Complications of vaginal myomectomy by posterior colpotomy. Eur J Obstet Gynecol Reprod Biol. 2008; 138:100–4.
29. Plotti G, Plotti F, Di Giovanni A, et al. Feasibility and safety of vaginal myomectomy: a prospective pilot study. J Minim Invasive Gynecol. 2008;15: 166–71.
30. Faivre E, Surroca MM, Deffieux X, et al. Vaginal myomectomy: literature review. J Minim Invasive Gynecol. 2010;17:154–60.

31. Yi YX, Zhang W, Guo WR, et al. Meta-analysis: the comparison of clinical results between vaginal and laparoscopic myomectomy. Arch Gynecol Obstet. 2011;283:1275–89.
32. Yu X, Zhu L, Li L, et al. Evaluating the feasibility and safety of vaginal myomectomy in China. Chin Med J (Engl). 2011;124:3481–4.
33. Rolli R, Favilli A, Acanfora MM, et al. Vaginal myomectomy is a safe and feasible procedure: a retrospective study of 46 cases. J Obstet Gynaecol Res. 2012;38:1201–5.
34. Deval B, Rousset P, Kayani S. Vaginal myomectomy for a thirteen-centimeter anterior myoma. Case Rep Obstet Gynecol. 2013;2013:285243.
35. Terzic M, Maricic S, Dotlic J. Vaginal removal of very large nascent uterine myoma – case report and literature review. Geburtshilfe Frauenheilkd. 2013;73: 724–6.
36. Agostini A, Beerli M, Franchi F, et al. Garnerella vaginalis bacteremia after vaginal myomectomy. Eur J Obstet Gynecol Reprod Biol. 2003;108:229.
37. Kalloo AN, Singh VK, Jagannath SB, et al. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. Gastorintest Endosc. 2004;60:114–6.
38. Nezhat F, Brill AI, Nezhat CH, et al. Adhesion formation after endoscopic posterior colpotomy. J Reprod Med. 1993;38:535–8.
39. Delveaux G, Devroey P, De Waele B, Willems G. Transvaginal removal of gallbladders with large stones after laparoscopic cholecystectomies. Surg Laparosc Endosc. 1993;3:307–9.
40. Ott V. Ventroscopia. Zh Akussherstva Bolezn. 1901; 15:1045–9.
41. Klaften E. Culdoscopy. Am J Obstet Gynecol. 1948;55:1071.
42. Decker A, Cherry T. Culdoscopy: a new method in diagnosis of pelvic disease. Am J Surg. 1944;64: 40–4.
43. Gordts S, Campo R, Rombatous L, Bronsen I. Transvaginal salpingoscopy: an office procedure for infertility investigation. Fertil Steril. 1998;70:523–6.
44. Tsin DA. Culdolaparoscopy a preliminary report. JSLS. 2001;5:69–71.
45. Tsin DA, Colombero L, Mahmood D, Padouvas J, Manolas P. Operative culdolaparoscopy: a novel approach combining operative culdoscopy and minilaparoscopy. J Am Assoc Gynecol Laparosc. 2001;8: 438–41.
46. Tsin DA, Colombero LT, Lambeck J, Manolas P. Minilaparoscopy assisted natural orifice surgery (MANOS). JSLS. 2007;11:24–9.
47. Ghezzi F, Raio L, Mueller MD, Gyr T, Buttarelli M, Franchi M. Vaginal extraction of pelvic masses following operative laparoscopy. Surg Endosc. 2002;16: 1691–6.
48. Tsin DA. The access in natural orifice transvaginal endoscopic surgery. In: Andrea T, editor. Laparoscopic entry: traditional methods, new insights and novel approaches. London: Springer; 2012.

Myoma in Pregnancy

15

Linnea R. Goodman, Lindsey N. Valentine, and Tommaso Falcone

Introduction

Uterine myomas (leiomyomas or fibroids) are common benign tumors, arising from the smooth muscle of the uterus. The true prevalence of fibroids is unknown as there is no screening program for asymptomatic women, but the estimated prevalence of myomas is 30 % in all women, 20–40 % in reproductive aged women and 40–60 % of women by age 35 [1]. The risk of myoma increases significantly with increasing age, and by age 50, 70–80 % of women will have had a fibroid [2]. Prevalence is two to three times higher in black women [3]. Decreased incidence is observed with increased parity. This effect is further amplified with childbearing from age 25 to 29 [1]. Factors that alter estrogen levels also modify risk. Smoking, exercise, and lean body mass decrease the incidence, while obesity and early menarche increases the risk. Despite strong associations with estrogen, there is no observed effect with oral contraceptives (Fig. 15.1) [1, 3]. Myomas are typically classified as one of three types: subserous, intramural or submucous, determined by location relative to the myometrium. Further descriptors include pedunculated, for those attached by a stalk, or cervical, based on location (Fig. 15.2).

Myomas are highly sensitive to, and dependent on, estrogen and progesterone. This is reflected in the prevalence during reproductive years and regression after menopause (Fig. 15.3) with cessation of ovarian activity. Myoma tissue maintains an elevated concentration of estrogen, from ovarian production and from local conversion by abundant aromatase within myoma cells. Progesterone is responsible for cell proliferation and cell growth. Activation of estrogen receptor α (alpha), present in myoma tissue, allows and enhances tissue response to progesterone [2].

With the increasing number of women pursuing childbearing later in life, improved ultrasound technology and widespread use of prenatal ultrasound, there has also been an increase in documented fibroids during pregnancy [4]. It has been reported that fibroids are present in 1.6–4.7 % of pregnancies [5].

Fibroids and Infertility

Pain, bleeding and bulk symptoms have been proven attributable to fibroids (Fig. 15.4), however, the impact of fibroids on fertility has been difficult to establish. As stated, it is estimated that fibroids are present in 20–40 % of reproductive aged women, but have only been identified in

L.R. Goodman, MD (✉) • L.N. Valentine, MD
T. Falcone, MD
Department of Obstetrics and Gynecology,
Cleveland Clinic, 9500 Euclid Avenue, A81,
Cleveland, OH 44195, USA
e-mail: Linnea.Goodman@gmail.com;
Lindsey.N.Valentine@gmail.com; Falcont@ccf.org

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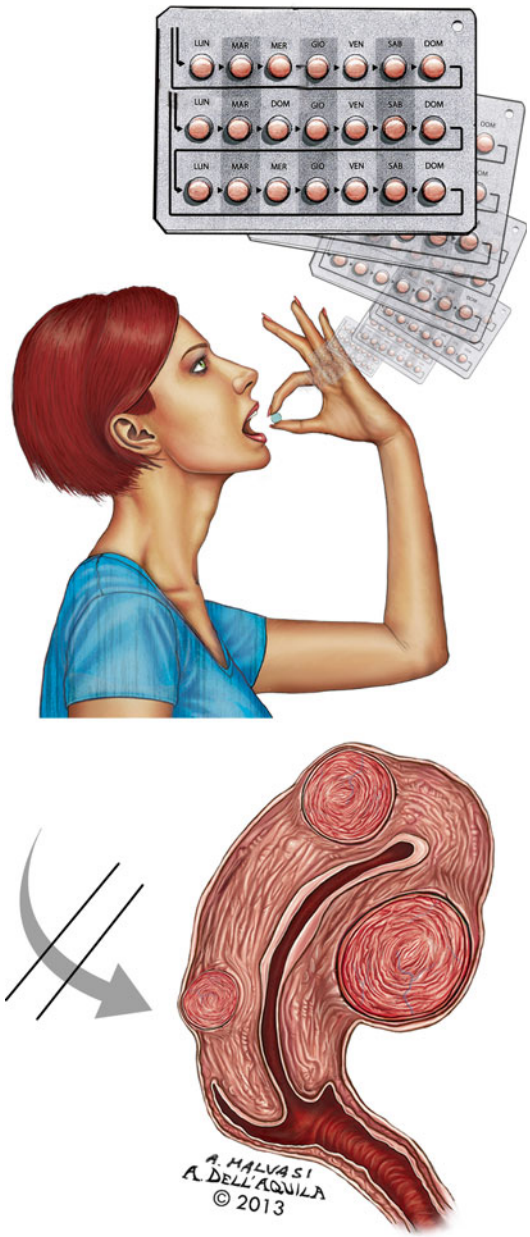

Fig. 15.1 Oral contraceptives do not modify the risk of myomas and do not influence their growth

5–10 % of infertile women [6]. Studying the relationship of fibroids to fertility is further complicated by the heterogeneous nature of fibroids including size, location, composition and number.

When considering the impact a fibroid may have on fertility, location is of utmost importance. Proposed mechanisms based on location include fibroid displacement of the cervix impacting sperm exposure, deformity of the uterine cavity interfering with implantation and gamete transport, obstruction of the tubal ostea, distortion of adnexal anatomy, impaired contractility of surrounding myometrium altering sperm or embryo transport and altered endometrium overlying fibroids impairing implantation [7]. Common themes among these proposed mechanisms include decreased fertility due to impaired sperm or oocyte transport and decreased embryo implantation. Based on this notion, it makes sense that the closer the fibroids are to the endometrial cavity, the greater the impact on fertility (Fig. 15.5).

This is evident in the literature. The majority of studies evaluating the effect of fibroids on fertility has focused on reproductive outcomes of patients with unexplained infertility before and after myomectomy or the presence of fibroids in women undergoing IVF cycles since these settings can best control for confounding factors. In both of these instances, there is resounding data that submucosal fibroids negatively impact clinical pregnancy (OR = 0.3, CI = 0.1–0.7) and delivery rates (OR = 0.3, CI = 0.1–0.8) [7–12], and are attributable to a three times increased risk of miscarriage [10, 11]. The relationship of intramural fibroids and infertility is less defined. Studies evaluating IVF outcomes in women with and without intramural fibroids have been inconsistent. Some studies, including a 2005 systematic review evaluating six studies, found intramural fibroids were attributable to significantly decreased implantation (OR = 0.62, CI = 0.48–0.8) and live birth rates (OR = 0.69, CI = 0.5–0.95) [8]. This was supported by a 2007 meta-analysis of seven studies again showing a decreased pregnancy (OR = 0.8, CI = 0.6–0.9) and delivery rate (OR = 0.7, CI = 0.5–0.8) [9]. Twenty-three studies compiled in a 2009 systematic review of the literature on the topic found that fertility outcomes were decreased in women with intramural fibroids including a decreased clinical pregnancy rate (RR 0.8, CI 0.7–0.94) and increased rate of spontaneous abortion (RR 1.75, CI 1.23–2.49) [11]. Alternatively, other studies have failed to

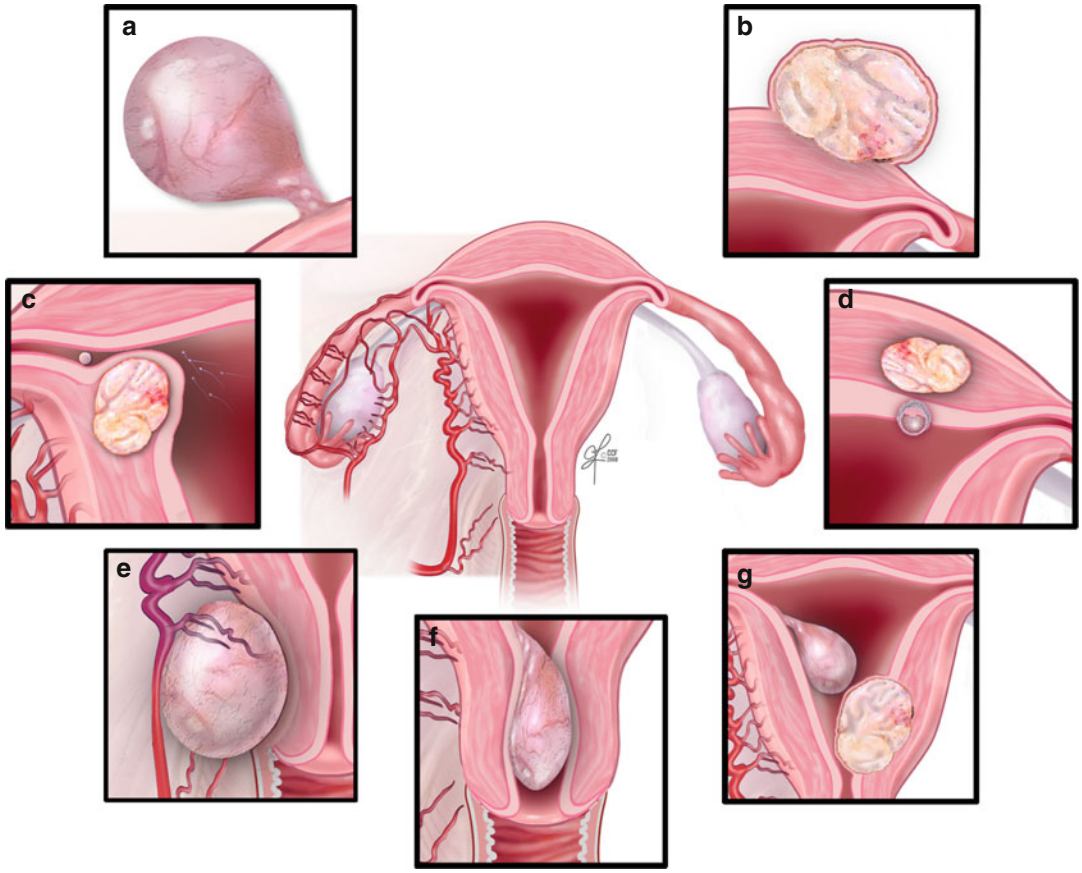

Fig. 15.2 Classification of fibroids; (**a**) – pedunculated; (**b**) – subserosal; (**c**) – submucosal; (**d**) – Intramural; (**e**) – within the broad ligament; (**f**) – cervical; (**g**) – intracavitary

Fig. 15.3 Myomas generally undergo a volumetric regression after menopause, as in post-menopausal patients needing transdermal hormonal replacement therapy

show a significant effect of intramural fibroids on IVF outcomes [10, 13–18]. Data concerning subserosal fibroids and fertility is more consistent showing no evidence of significant deleterious effects on clinical pregnancy and implantation rates and no increased risk of miscarriage [11].

In conclusion in regard to location, there is evidence that intracavitary and submucosal fibroids may have a negative effect on IVF success and miscarriage rates, that data on intramural fibroids are controversial and that subserosal fibroids likely have no adverse impact on fertility. However, the size and number of fibroids must be considered with larger size and multiple myomas having a more significant effect on fertility, regardless of location [13, 19, 20].

Just as there is not a clear cut consensus on the effect of fibroids on fertility, treatment of

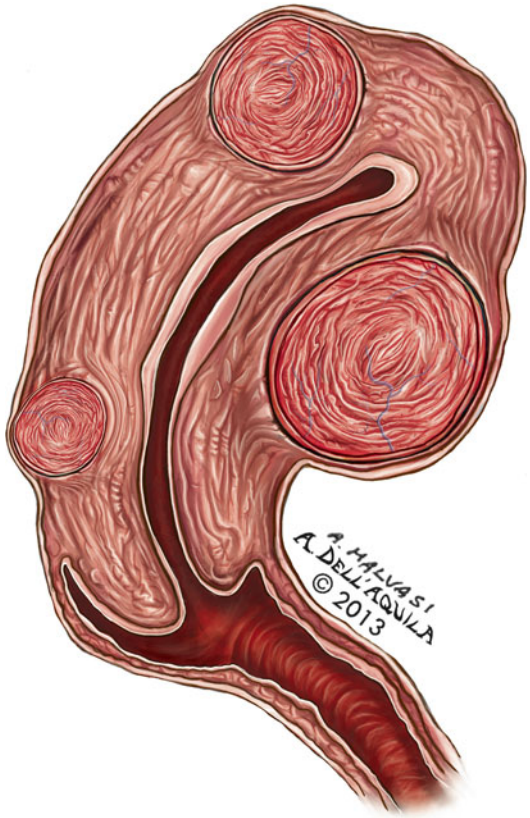

Fig. 15.4 The uterine myomas may cause pain, bleeding and bulk symptoms

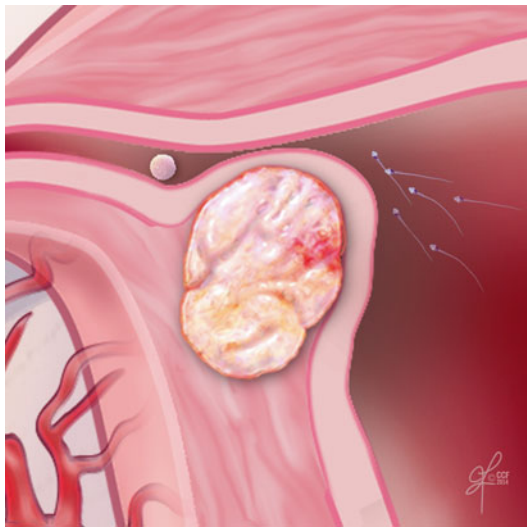

Fig. 15.5 Submuscosal fibroid blocking tubal ostea and/or impairing oocyte and sperm transport

fibroids to improve fertility is controversial. Medical management of fibroids is often counterproductive to conceiving and surgical treatment can incur risks both to the health of the patient and for future fertility. The most straightforward circumstance involves the submucosal fibroid with clear distortion of the uterine cavity. The treatment of submucosal fibroids can generally be achieved by hysteroscopic myomectomy (Fig. 15.6). This has lower risks than intra-abdominal surgery, but has the significant risk of developing scar tissue within the uterus that can impede future fertility. The previously mentioned 2009 systematic review showed a twofold increase in clinical pregnancy rates in IVF after myomectomy of submucosal fibroids compared to women without fibroids [11]. There have also been randomized trials comparing expectant management of fibroids compared to treatment with myomectomy with a significant increase in pregnancy rates among patients with submucosal fibroids [21]. When weighing the risks and benefits of surgical management of cavity-distorting submucosal fibroids in regards to fertility, it seems prudent to offer myomectomy to improve reproductive outcomes.

The treatment of intramural fibroids to improve fertility outcomes is debated as their effect on fertility is less clear. Again, size and number play a role in determining the beneficial effects of surgical treatment. Small, single intramural fibroids have less of an effect on fertility; therefore surgical risks may outweigh the benefits in these patients. Alternatively, there was a cohort study showing that in women with at least one intramural fibroid greater than 5 cm in size, myomectomy significantly improved clinical pregnancy and live birth rates after up to three IVF cycles [22]. However, there are also studies with contradicting results, showing no benefits of myomectomy of intramural fibroids in asymptomatic infertile couples. It appears that in these patients the duration of infertility and other confounding fertility factors have a greater effect on fertility outcomes rather than the size or location of the largest fibroid surgically removed [23, 24].

It is in the management of these patients, infertile women with asymptomatic intramural

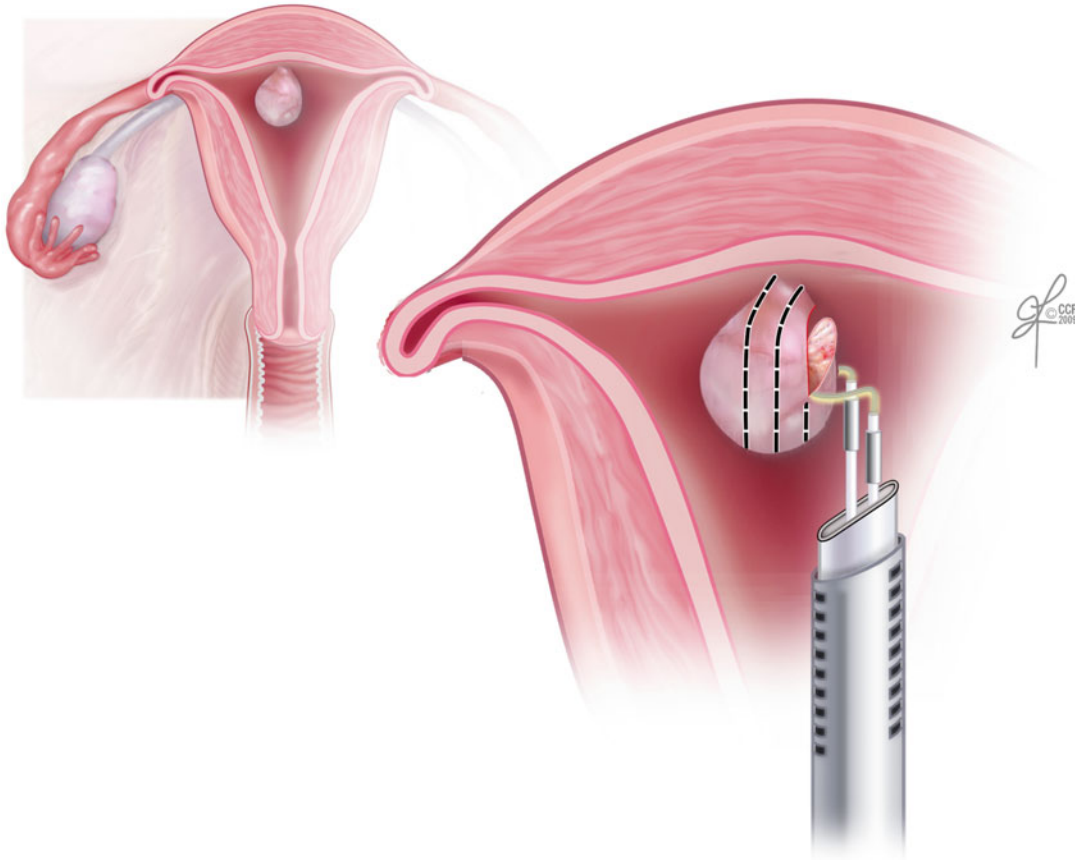

Fig. 15.6 Hysteroscopic resection of an intracavitary fibroid

fibroids, that it is essential that surgical complications must be carefully considered. Since it has not been concretely established that intramural fibroids have a deleterious effect on fertility, and surgical complications such as pelvic and adnexal adhesions, intra-abdominal infections and intrauterine scarring can negatively affect fertility, surgical management must be thoughtfully considered. Age of the patient, infertility history and planned fertility treatments contribute to this decision, as well as size, location and number of the fibroids. Large intramural fibroids that distort the uterine cavity may have the same negative effect on fertility as submucosal fibroids, while smaller fibroids with no endometrial involvement likely do not. Adhesion formation will also be affected by location of myomectomy, with cornual or posterior fibroids of more concern than fundal or uterine body ones.

While the surgical removal of submucosal fibroids by hysteroscopic myomectomy will likely improve fertility outcomes, intramural myomectomies need to be carefully considered and intra-abdominal removal of subserosal fibroids likely pose no benefit to infertile women. In addition, asymptomatic women with untested fertility may want to attempt conception prior to surgical management of any fibroids as they may not warrant any treatment.

Regardless of fibroid location, when attempting successful surgical management for fertility purposes, it is imperative to use meticulous surgical technique to decrease complications and lead to the best surgical and fertility related outcomes. Careful tissue handling, adequate hemostasis, less exposed suture and minimal tissue trauma can lead to improved results. When fibroids are completely or mostly submucosal

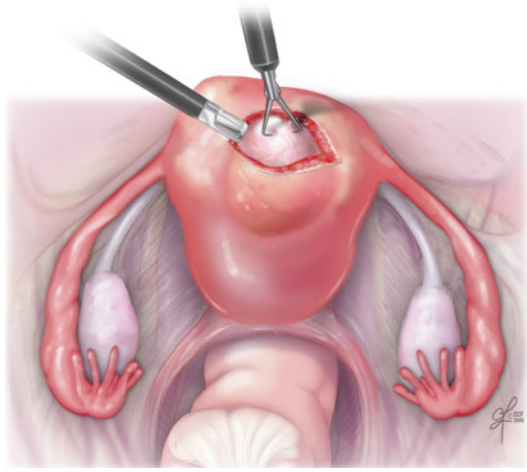

Fig. 15.7 Myomectomy by minimally invasive method

in location, myomectomy can be performed hysteroscopiclly. Intramural fibroids require intra-abdominal entry which can be obtained in one of three ways. Open surgery by mid-line, pfannenstiel or 'minilaparotomy' incision has been a mainstay of gynecologic surgical technique. Myomectomy can also be performed by laparoscopic and/or robotic methods with similar final outcomes with the advantage of decreased blood loss, decreased postoperative pain, shorter hospitalizations and shorter overall recovery time [25–28] (Fig. 15.7). In 2007, there was a multicenter, randomized trial looking at reproductive outcomes after minilaparotomy and laparoscopic myomectomy that found no significant differences in clinical pregnancy, live birth and spontaneous abortion rates between the two surgeries in women with otherwise unexplained infertility [26].

In conclusion, submucosal fibroids likely have a significant effect on fertility and patients can potentially benefit from generally low risk hysteroscopic surgical removal. Intramural fibroids, however, may have a negative impact on fertility, but this depends on their location, size and number and surgical removal can be considered in patients with long-standing otherwise unexplained infertility as long as surgical risks and benefits are thoughtfully compared. Subserosal fibroids likely have no effect on fertility and only should be removed if the patient is otherwise symptomatic. Each patient must be uniquely considered when evaluating for surgical management of fibroids to improve fertility outcomes and be aware of the risk-benefit profile.

Diagnosis and Monitoring of Fibroids in Pregnancy

The majority of fibroids in pregnancy are diagnosed incidentally on routine obstetric ultrasounds as it is been reported that during pregnancy, clinical exam can only detect 42 % of fibroids >5 cm, and that drops to a dismal 12.5 % when they are <5 cm [29]. When a mass is suspected, ultrasound is non-invasive, relatively inexpensive, fast, widely available and safe in pregnancy making it the first line imaging technique. In skilled hands, ultrasound can predict the nature of a pelvic mass with over 80 % accuracy, and can provide helpful information such as size, shape, consistency and location [29].

MRI is another imaging modality that adds value during pregnancy, allowing for a more precise and reproducible mapping of fibroid location and size. This is particularly helpful when there is diagnostic inconsistencies or for use in surgical planning. Unfortunately, the use of MRI is limited by availability, expense and need for experienced observers [30].

When detected incidentally, fibroids only need to be followed by serial imaging if there is concern for fetal development, utero-placental insufficiency due to fibroid location in close proximity to the placenta, surgical planning in the event of a planned cesarean section or obstruction of the birth canal. In the event of pain, ultrasound and/or MRI can be useful to rule out other intra-abdominal causes, to diagnose fibroids and to evaluate for fibroid torsion [31].

Course of Fibroids in Pregnancy

Given that myomas are estrogen and progesterone sensitive, it has been theorized that fibroids would increase in size during pregnancy, due to elevated serum estrogen levels. However, studies have shown that the majority of myomas

undergo no significant change in volume [32]. Interpretation of change in size can be difficult, because myomas often change shape during pregnancy, becoming more flattened and elongated as the uterus grows and stretches [32]. As a result, more recent studies have focused on changes in fibroid volume, rather than diameter which may be misleading. Prospective studies utilizing serial ultrasound to assess the change in fibroids during pregnancy have shown that most (60–78 %) do not increase in volume [33, 34]. Contrary to popular thought, some myomas may even decrease in size throughout the course of pregnancy [32–37]. Data revealed 40–64 % show some decrease in volume, with larger myomas (defined as diameter >4 cm) being more likely to decrease, particularly after 30 weeks [37, 38].

Although there has been some inconsistency in results, fibroid growth during pregnancy is much rarer than once thought. When increases do occur, they tend to be during the first trimester [32–34, 36] and are quite small in magnitude, with the maximum observed difference <25 % of initial volume [33, 34]. Overall, changes in size remain difficult to predict as fibroids may remain unchanged, enlarge or decrease in volume during pregnancy. Nonetheless, these changes are typically small with limited clinical implications.

Few studies have assessed change in fibroids extending into the post-partum period, but available data suggests a decrease in size after delivery [32, 33]. In a prospective study by Laughlin et al., 79 % of identified fibroids decreased in size compared to their early-pregnancy scan [35]. There was a greater change in diameter of fibroids in the lower uterine segment, where there is a larger degree of uterine stretching. However, this study calculated change in size from measured diameter, which may overestimate the true change in fibroid volume, as discussed previously [35].

Complications of Fibroids in Pregnancy

Most women with fibroids remain asymptomatic with uncomplicated pregnancies. While the true effects of fibroids on pregnancy remain uncertain, it has been estimated that 10–40 % of patients with myomas will experience a complication [39].

Obstetric Complications

First Trimester Complications

As outlined above, there has been extensive research examining the effects of fibroids on fertility. There have been comparatively few studies, however, evaluating the effects of fibroids on recurrent first trimester pregnancy loss, and what studies there are do not show that the majority of fibroids can be implicated as a cause of this devastating condition. Despite the lack of evidence, there have been a number of proposed mechanisms linking fibroids to recurrent pregnancy loss, all centered on fibroids as a cause of decreased regional blood flow [40].

As in infertility research, the majority of data concerning fibroids related to recurrent pregnancy loss compare women before and after myomectomy [41, 42], or from a compilation of studies examining women undergoing IVF cycles for infertility. One retrospective study concluded that fibroids were associated with an increased rate of pregnancy loss by determining a 60 % rate of miscarriage in women with fibroids that decreased to 24 % after myomectomy [42]. Other studies have consistently shown that submucosal fibroids have the greatest effect on first trimester pregnancy loss when compared to fibroids in other locations, and subsequently should be removed to improve pregnancy outcomes [13, 15, 16, 43]. Generally, submucosal fibroids are singular and smaller than their intramural counterparts and generally are amenable to hysteroscopic resection, making the recommendation for removal an easier decision since the risk profile is low [23, 44–47].

Because the data is inconclusive on whether intramural fibroids may contribute to recurrent spontaneous first trimester pregnancy loss, the risk-benefit ratio of intra-abdominal surgery must be considered when evaluating these patients for treatment. When fibroids have a definitive effect on the intrauterine cavity, they may warrant removal to assist in reproductive outcomes, and

when they clearly are separate, removal may not provide any therapeutic benefit [48].

Second and Third Trimester Complications

The most common second and third trimester obstetric complications reported are pain, preterm labor, and fetal malpresentation. Studies have also questioned a relationship between fibroids and placental abruption, placenta previa and intrauterine growth restriction, with conflicting results. Factors associated with a higher risk of complications are fibroid size, location, number, and location relative to placenta implantation.

Fetal malpresentation is one of the more commonly cited outcomes associated with fibroids in pregnancy [5, 49]. Fibroids, particularly those that are submucosal, can distort the uterine cavity and lead to fetal malpresentation [3]. Cumulative data from a review showed 13 % of patients with fibroids had malpresentation, compared to 4.5 % in non-fibroid pregnancies (OR, 2.9; 95 % CI, 2.6–3.2) [10]. This risk, specifically breech presentation, was further increased with larger fibroid volume (>100 mm^3) [5] or size (>10 cm) [49].

Uterine fibroids have been associated with an increased risk of preterm labor and delivery (<37 weeks) [49–51]. Studies have indicated a positive correlation with preterm delivery and myoma volume [52]. It has also been suggested that the presence of multiple fibroids may be associated with a higher risk of preterm contractions [50]. The mechanism behind this association is not well understood. One popular theory suggests that the presence of myomas inhibit normal distension of the uterus [5, 49].

Fibroids have been investigated as a cause of intrauterine growth restriction. Most studies have shown no correlation [5, 50]. However, evidence is inconsistent and some authors report a higher incidence of small-for-gestational age infants with increased fibroid volume [10].

Similarly, there are conflicting results regarding placental abnormalities in the presence of fibroids. Some studies report greater risk of placental abruption with fibroids. A more significant risk is suggested with those fibroids that have an increased volume or retroplacental location [3, 10]. Other studies challenge these results, with no observed correlation [52]. There is no evidence to support an association with placenta previa, despite belief that disruption of the uterine cavity could result in lower uterine placental implantation [10].

Non-Obstetric Complications

The majority of fibroids are asymptomatic during pregnancy and do not require treatment, however, when fibroids undergo 'red-degeneration,' torsion or impaction, they may be the cause of severe localized abdominal pain and require immediate workup and treatment in pregnancy.

Red or carneous degeneration is the most common non-obstetric complication of fibroids in pregnancy and can occur in up to 5 % of pregnant women with fibroids [52]. Corresponding with the times of greatest growth, red degeneration most commonly occurs in the first or early second trimester of pregnancy. There are a few proposed pathophysiologic mechanisms as to why red degeneration causes severe pain. One is that with rapid growth seen in early pregnancy, the fibroid outgrows its blood supply leading to ischemia, necrosis and infarction [53, 54]. Another proposed mechanism is that the shift in architecture of the growing uterus can cause kinking, distortion or obstruction of the blood supply to the fibroid, even in the absence of significant growth [1]. Along with the two above mechanisms is the thought that the release of prostaglandins from cellular damage associated with fibroid infarction may result in severe pain.

The diagnosis of red degeneration is often made clinically by acute onset localized abdominal pain over a known fibroid location. Pain is the defining feature, but it may also be associated with nausea, vomiting, low-grade fever, and leukocytosis. The diagnosis is one of exclusion, and complications of pregnancy such as preterm labor, placental abruption, pyelonephritis and other intra-abdominal pathology such as appendicitis, nephrolithiasis and constipation must

be ruled out. Ultrasound can provide helpful diagnostic clues including anechoic cystic spaces or coarse heterogeneous echogenic patterns within the degenerating fibroids [38].

The mainstay of treatment for red degeneration in pregnancy is conservative management with hospitalization, rest, hydration, and symptomatic analgesia. Non-steroidal anti-inflammatory (NSAID) medications have the best success rates in controlling pain associated with this condition, but must be used with caution, especially in the later part of pregnancy due to neonatal concerns of fetal premature closure of the ductus arteriosis, nephropathy, pulmonary hypertension, necrotizing enterocolitis and oligohydramnios [55]. If a short course (<48 h) of NSAIDs is unsuccessful in managing pain, narcotic pain medication may need to be used sparingly, however has constipating side effects, which may compound the abdominal pain. Epidural analgesia has also been reported with good pain results in severe cases refractory to medical management [56].

Surgical Management of Fibroids in Pregnancy

Although many review articles have been written about the surgical management of fibroids [57], they rarely contain information on the surgical management of fibroids in pregnancy. Conservative management of red degeneration of fibroids in pregnancy is the preferred method of treatment and is often successful. Rarely, though, pain is refractory to medical management or cellular necrosis leads to an acute abdomen with peritoneal signs and surgical management can be considered for treatment of a necrotic or torsed pedunculated fibroid (Fig. 15.8, Table 15.1). Ultrasonographic doppler flow is often inconclusive in the diagnosis of these patients and MRI may be helpful to characterize the size and location of the fibroid as well as the extent of the fibroid stalk for presurgical planning [31]. Careful consideration must be performed prior to taking a patient to surgery as there are increased risks associated with myomectomy during pregnancy. Increased blood flow to and throughout the uterus during pregnancy can lead to significant hemorrhage and surgical entry into the abdomen and uterus can pose fetal risks including preterm labor and fetal distress [58] (Fig. 15.9).

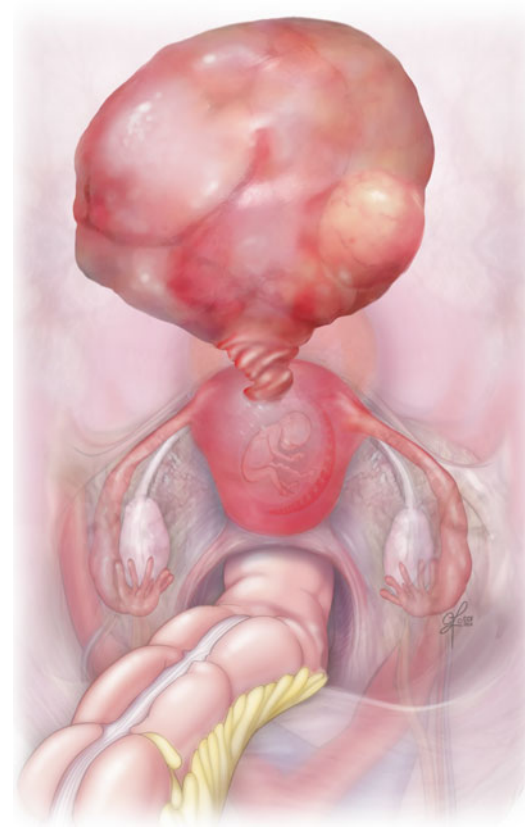

Fig. 15.8 Torsed pedunculated fibroid on a pregnant uterus

Table 15.1 Indications for surgery

Conservative management	Surgical candidate
Known fibroids	Severe pain with unknown diagnosis
Non-acute abdomen	Acute abdomen
Pain responsive to analgesia	Evidence of fibroid torsion on imaging
Improvement in pain over time	Pain unresponsive to conservative measures

Previously, laparotomy had been the surgical method of choice for myomectomy during pregnancy due to the concern of entry and insufflation of a gravid abdomen [58–61]. However, more recently there have been multiple case reports of successful minimally invasive laparoscopic myo-

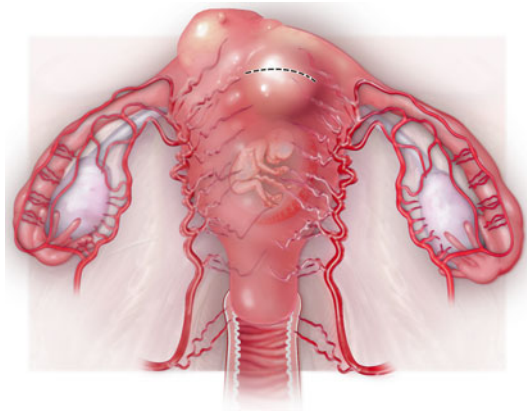

Fig. 15.9 Blood supply to a pregnant uterus

Table 15.2 Special considerations for laparoscopic surgery in pregnant patients

Consideration	Options
Patient positioning	Left lateral tilt
Initial port placement	Umbilical Supra-umbilical Left upper quadrant
Mode of entry	Hassan technique Verees needle Optiveiw trocar
Number of additional ports	2–4
Operative technique	Decreased insufflation pressure Decreased Trendelenburg Slow position changes Decreased uterine manipulation
Method of fibroid ischemia	Coagulation Suture/endoloop Vascular stapler
Fibroid removal	Mini-laparotomy Morcellation
Fetal monitoring	None, intermittent or continuous based on gestational age

mectomies during the first and second trimesters of pregnancy [62–66] allowing for shorter recovery times, less blood loss, earlier ambulation and less narcotic use post-operatively. There are certain precautions and special considerations proposed for minimally invasive surgery in this unique surgical population (Table 15.2).

The choice of trocar placement and entry must be carefully considered due to the underlying gravid uterus. Umbilical, supraumbilical or left upper quadrant point of entry have been described based on fundal height and fibroid location. Case reports describing laparoscopic myomectomy at 11, 14 and 25 weeks reported infraumbilical, umbilical and 5 cm supraumbilical port entry respectively [62, 63, 66]. Method of entry including initial Verees needle for pneumoperitoneum followed by blind entry and use of the 'Hassan' or open technique of laparoscopic entry have both been described based on surgeon preference [62–66]. While there has not been extensive experience with laparoscopic myomectomy during pregnancy, laparoscopic cholecystectomy and appendectomy have been performed for many years with good success rates and few complications and both methods of entry appear safe [67]. Despite different preferences in initial entry, it is agreed upon that additional ports must be placed under direct visualization. The choice of number and placement of additional ports is again dependent on surgeon preference, with the majority of cases describing two to four additional ports based on fibroid size and location for retraction, visualization and ease of suturing. Additional ports may be helpful to minimize manipulation of the uterus with utmost care during retraction, pushing and pulling as to not disrupt blood flow or damage the uterus (Fig. 15.10).

The choice of a 0 or 30° laparoscope may also be used to assist in visualization and decrease manipulation of the uterus.

Patient positioning before and during surgery can help to decrease the risk of utero-placental insufficiency. Initial positioning of the patient in left-lateral tilt and slow change in and out of the least possible amount of Trendelenburg needed to complete the surgery may assist in keeping adequate blood flow to the uterus. In addition, slow insufflation of carbon dioxide gas at lower pressures (10 mmHg vs. 15 mmHg) can help to avoid carbon dioxide absorption leading to acid-base disturbances [66].

There are a number of intra-op surgical considerations as well. The location of laparoscopic myomectomy incision should be well planned with consideration of imminent suture closure, as it is generally considered easier to suture in the

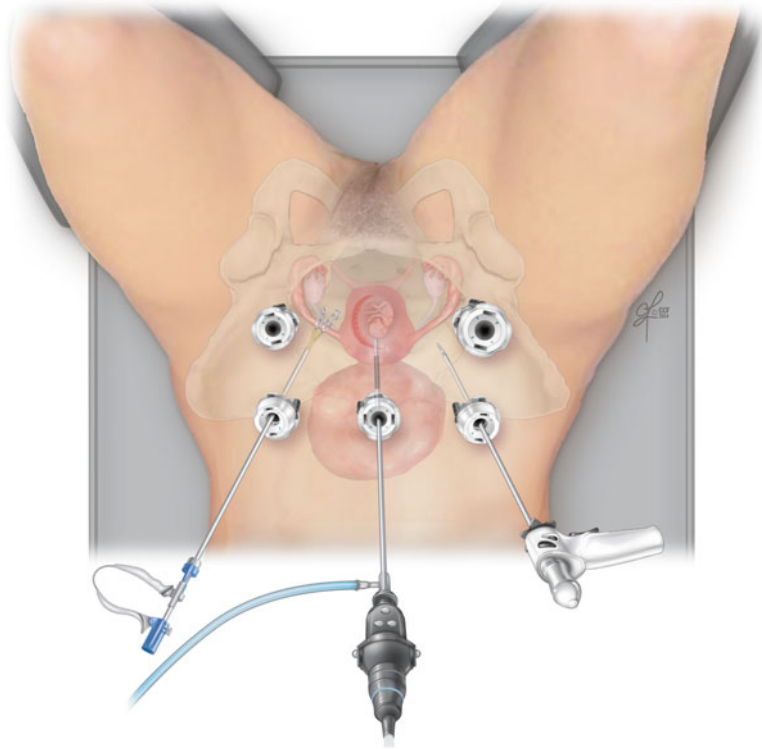

Fig. 15.10 Careful consideration of port placement in a pregnant patient

horizontal plane. Multiple methods of fibroid ischemia and separation from the uterus have been described including careful dissection with cautery at the base [63], strangulation with Monocryl suture [62], use of an Endoloop suture [67] and the use of an endoscopic vascular stapling device [66]. All methods attempt to minimize blood loss while limiting the use of monopolar electric and bipolar current to decrease the risk of electro-surgical damage.

Myomectomy during pregnancy is a high risk surgery owing to the increased vascularity and cardiac output during pregnancy, however many methods of reducing blood loss employed during myomectomy in non-pregnant patients should not be used in pregnancy. Vasopressin has not been studied in pregnant patients, while other agents designed to decrease blood loss such as misoprostol should not be used secondary to risk of pre-term labor and the use of a uterine tourniquet is obviously contraindicated.

Once separated, the fibroid may be removed either through minilaparotomy or by morcellation. Both methods have been described in case reports of myomectomy during pregnancy without complication. While morcellation allows for maximum benefit of minimally invasive surgery, it must be performed with utmost caution due to decreased intra-abdominal space and visibility secondary to the enlarged gravid uterus.

The laparoscopic myomectomies described in the literature have all been pedunculated, therefore accomplished without large incisions on the uterus that needed closure. Consequently, there is little described regarding closure method or suture type for myomectomy during pregnancy. Should the incision need closure, the same considerations of laparoscopic myomectomy incision closure in non-gravid patients should then be applied – multilayer closure with delayed resorbable suture to ensure adequate closure of the dead space and hemostasis with minimal exposed suture to prevent adhesions.

Accidental entry into the amnion has not been reported as of yet during laparoscopic myomectomy; however, there are reports of iatrogenic

amnionic entry during other laparoscopic procedures in pregnancy [68]. If the puncture site is small (i.e. Verees needle puncture) it will likely seal on its own, just as an amniocentesis puncture site. A larger puncture site may need physical closure with delayed resorbable suture as described in open fetal surgery procedures [69]. A skilled laparoscopic surgeon may be able to perform this without conversion to laparotomy if there is adequate visualization; however, data on this is limited.

Other complications of laparoscopic surgery during pregnancy have been described, such as one case of pneumoamnion resulting in a fetal loss in one patient undergoing diagnostic laparoscopy at 21 weeks gestation [70]. There has also been a case of uterine septic necrosis following laparoscopic myomectomy which necessitated re-exploration, debridement of uterine tissue, and suture closure of a three centimeter uterine defect with clearly visualized amnion [67]. These cases strengthen the argument that conservative management of fibroids in pregnancy is preferred and each patient must carefully consider the risks and benefits before proceeding with laparoscopic myomectomy during pregnancy.

There have been no reports to date of robotic assisted laparoscopic myomectomies performed during pregnancy, likely due to minimal added benefit of the robot with additional risks of longer surgery times, increased Trendelenburg position and additional port sites. Although, robotic assisted abdominal cerclage placement has been performed successfully during the first trimester of pregnancy [71] indicating that in special circumstances the robot may be able to be used for robotic myomectomy during pregnancy if needed [25, 27].

Management of Fibroids During Labor and Delivery

Early diagnosis of large fibroids in pregnancy can provoke anxiety regarding mode of delivery, however their presence should not be considered a contraindication to a trial of labor. If there is concern, fibroid location and size should be evaluated close to term. The patient should be informed of the increased risk of cesarean section with the potential for low fibroids to obstruct the birth canal and the increased risk of complications during cesarean section with anterior fibroids in the lower uterine segment. Due to the increased risks, preemptive planning can include ensuring the patient has adequate blood counts and iron stores, having cross matched blood products on hand and planned careful observation of labor progress [72].

In patients with previous myomectomy prior to pregnancy, there is extensive debate as to who should be offered primary elective cesarean section versus trial of labor. While there have been several case reports of uterine rupture, both spontaneous and during labor, after myomectomy [73–76], there are no specific recommendations regarding this topic. In 2012, the Maternal Fetal Medicine Units network conducted a study comparing women with previous myomectomy or classical cesarean section to those with previous low-transverse cesarean section looking at rates of uterine rupture and placenta accreta [77]. Of the 176 women with prior myomectomy, there were no cases of uterine rupture or placenta accreta, calling into question the common practice to recommend cesarean section to pregnant patients with previous myomectomy, particularly in those whose uterine cavity was entered during surgery.

Of the data available, surgical route of myomectomy, open laparotomy versus minimally invasive methods, shows no difference in future pregnancy rates and outcomes [26, 28, 78]. Some recent studies have suggested that laparoscopic myomectomy may put patients at increased risk of uterine rupture compared to a laparotomic approach [79], with the proposed mechanisms including method of myomectomy incision closure, suture choice and use of electrocautery [80]. However, in these studies the absolute risk of uterine rupture remained low (0.5–1 %) and the overall conclusion is that there is no difference. A retrospective study in 2013 examining 872 women who underwent robotic myomectomy resulting in 127 pregnancies and 92 deliveries had one

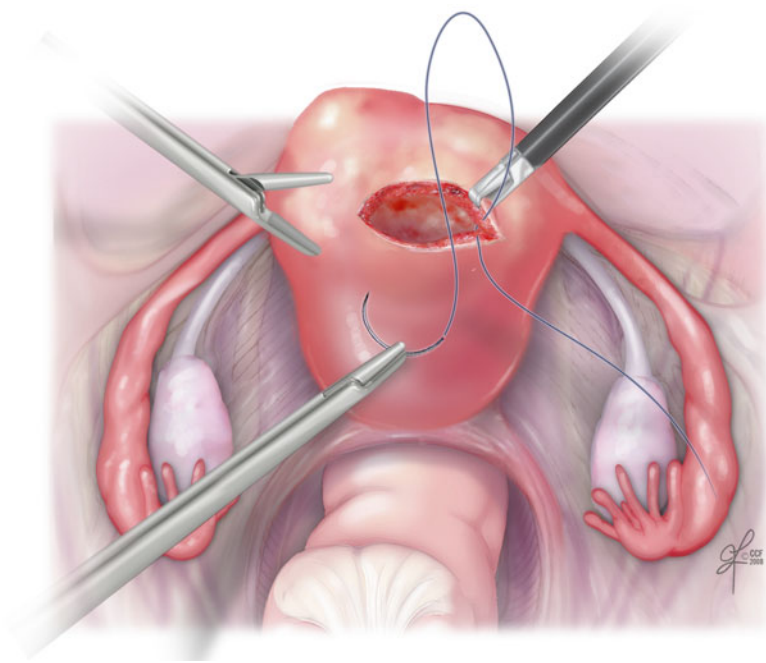

Fig. 15.11 Robotic closure of myomectomy incision

patient experience uterine rupture, again confirming a low absolute risk of uterine rupture regardless of fibroid size, location or entry into the cavity [81] (Fig. 15.11).

Extensive review of pregnancy after hysteroscopic myomectomy has revealed improved reproductive outcomes without significant deleterious effects [82, 83]. Barring recurrence of significant fibroid burden, these patients can safely undergo trial of labor without increased risks. Overall, it is important to review previous operative notes, current ultrasonographic assessment of the uterus and patient comorbidities and confounding factors and then have an informed discussion with the patient to determine the best route of delivery for each specific patient.

Cesarean Myomectomy

Traditional teaching strongly recommends avoiding myomectomy at the time of cesarean section, due to the risk of massive hemorrhage necessitating hysterectomy, and increased postoperative morbidity. Exception is made only for small pedunculated fibroids, or those directly in the cesarean incision. However, recent studies have suggested this approach be reconsidered, with evidence that successful removal of myomas during cesarean section can be completed safely in appropriately selected patients [84–90].

A meta-analysis of nine studies revealed that patients undergoing cesarean myomectomy had no statistically significant difference in postoperative hemoglobin, estimated blood loss, operative time, length of hospital stay, blood transfusion frequency or incidence of postoperative fever [90]. Although no serious complications were reported in any of these studies, the procedure is not without risk. Previous studies have reported ileus, extended hospital stay, and cases of massive blood loss requiring blood transfusion, uterine artery embolization or hysterectomy [90]. Various methods have been employed in an attempt to decrease bleeding and minimize risk. Most commonly, high dose or prolonged (up to 24 h) administration of oxytocin was used [84, 86]. Other described techniques include use of a tourniquet for intermittent ligation of the uterine artery [86, 90].

When considering long-term benefits, cesarean myomectomy may seem appealing to both

providers and patients. Cesarean myomectomy could improve symptoms in affected patients and reduce future surgery, including its associated risks and costs. One small study, following women with fibroids after cesarean delivery, found that within 38 months, 40.9 % had additional surgery for leiomyoma [90]. Some authors have also suggested that the relative size of myomectomy incision over the uterus may be smaller during pregnancy, given the greater growth of the uterus compared to myomas during pregnancy [86].

There is limited data available on selection of patients. Consideration should likely be given to symptoms, desire for future childbearing, size and location of fibroids. Myomas included in studies have been quite varied in both size and location. Some authors have recommended avoiding intramural, fundal fibroids [86].

While current data supports the feasibility and safety of cesarean myomectomy for certain patients, there is no consensus regarding management of myomas during cesarean section. Moving forward, the experienced provider should continue to approach cesarean myomectomy with caution, including careful evaluation and thorough counseling of individual patients.

Course of Fibroids After Pregnancy

Just as in pregnancy, the course of established fibroids postpartum is variable with the majority of women experiencing no significant change in fibroid burden or symptoms. There is some evidence, however, that the processes involved in late pregnancy, labor, delivery and postpartum may provide some protection from future development of fibroids and even some therapeutic effect of current fibroids likened to that of a uterine artery embolization. Proposed mechanisms include that the apoptosis and extensive remodeling of the myometrium postpartum may induce involution of fibroids or that fibroid blood supply may regress during uterine involution [91–93]. Along with involution of fibroids, restriction of blood supply to subserosal fibroids postpartum can also lead to ischemic degeneration and rarely a source of infection. Additionally, remodeling of the myometrium can induce sloughing of submucosal fibroids leading to bleeding and passing of products that may be confused with retained products of conception. Bleeding patterns, associated symptoms, lab testing and imaging may provide diagnostic clues to help differentiate the two.

If fibroids caused significant pain or complications during pregnancy, myomectomy can be considered prior to subsequent pregnancies. There is no consensus concerning optimal waiting period to try to conceive post-myomectomy, therefore the route and extent of the surgery must be considered. It is prudent to recommend at least a few months after hysteroscopic myomectomy to allow for endometrial wound healing as a recent study showed that on second-look hysteroscopy most patients did not have evidence of a healed endometrium until 3 months postoperatively [94]. Intra-abdominal myomectomy is less clear-cut as there is no direct method to evaluate intrauterine healing. Wound perfusion and dissolution of hematoma over uterine scars post myomectomy have been visualized on ultrasound in as little as 3 months [95–97], however, it is generally accepted to wait 6–12 months before recommending attempting conception or undergoing fertility treatments [98].

Conclusion

Fibroids in pregnancy are a common condition and the prevalence is likely to increase as women are delaying child bearing. Our knowledge of the impact of fibroids on fertility and reproductive outcomes is increasing with improved diagnostic tools and awareness, however management remains controversial. It appears that hysteroscopic resection of submucosal fibroids prior to pregnancy can improve outcomes, asymptomatic subserosal fibroids should be left alone and management of intramural fibroids depends on size, number, location, symptoms and patient profile.

Luckily, the majority of fibroids in pregnancy are asymptomatic and do not require treatment. When complications do arise, such as severe abdominal pain associated with red degeneration, conservative treatment is often successful. Myomectomy

during pregnancy is reserved for severe cases of a torsed or degenerating pedunculated fibroid, and can be accomplished by open or minimally invasive methods. Cesarean section should be performed for routine obstetric indications and with careful consideration, many patients with current fibroids and those with previous myomectomies can be offered a trial of labor.

Fibroids are the most common benign tumors encountered in women of reproductive age. However, there is a paucity of directive recommendations regarding management of fibroids for future fertility, during pregnancy and surrounding labor and delivery. Future randomized controlled trials are needed to assist in a consensus on the management of fibroids in this special patient population.

References

1. Parker WH. Etiology, symptomatology, and diagnosis of uterine myomas. Fertil Steril. 2007;87(4):725–36.
2. Bulun SE. Uterine fibroids. N Engl J Med. 2013; 369(14):1344–55.
3. Zaima A, Ash A. Fibroid in pregnancy: characteristics, complications, and management. Postgrad Med J. 2011;87(1034):819–28.
4. Hasan F, Arumugam K, Sivanesaratnam V. Uterine leiomyomata in pregnancy. Int J Gynaecol Obstet. 1991;34(1):45–8.
5. Stout MJ, Odibo AO, Graseck AS, Macones GA, Crane JP, Cahill AG. Leiomyomas at routine second-trimester ultrasound examination and adverse obstetric outcomes. Obstet Gynecol. 2010;116(5):1056–63.
6. Donnez J, Jadoul P. What are the implications of myomas on fertility? A need for a debate? Hum Reprod. 2002;17:1424.
7. Practice Committee of the American Society for Reproductive Medicine. Myomas and reproductive function. Fertil Steril. 2008;90 Suppl 5:125.
8. Benecke C, Kruger TF, Siebert TI, Van der Merwe JP, Steyn DW. Effect of fibroids on fertility in patients undergoing assisted reproduction. A structured literature review. Gynecol Obstet Invest. 2005;59:225.
9. Somigliana E, Vercellini P, Daguati R, Pasin R, De Giorgi O, Crosignani PG. Fibroids and female reproduction: a critical analysis of the evidence. Hum Reprod Update. 2007;13:465.
10. Klatsky PC, Tran ND, Caughey AB, Fujimoto VY. Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. Am J Obstet Gynecol. 2008;198:357–66.
11. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril. 2009;91:1215.
12. Pritts EA. Fibroids and infertility: a systematic review of the evidence. Obstet Gynecol Surv. 2001;56:483.
13. Farhi J, Ashkenazi J, Feldberg D, Dicker D, Orvieto R, Ben Rafael Z. Effect of uterine leiomyomata on the results of in-vitro fertilization treatment. Hum Reprod. 1995;10:2576.
14. Dietterich C, Check JH, Choe JK, Nazari A, Fox F. The presence of small uterine fibroids not distorting the endometrial cavity does not adversely affect conception outcome following embryo transfer in older recipients. Clin Exp Obstet Gynecol. 2000; 27:168.
15. Jun SH, Ginsburg ES, Racowsky C, Wise LA, Hornstein MD. Uterine leiomyomas and their effect on in vitro fertilization outcome: a retrospective study. J Assist Reprod Genet. 2001;18:139.
16. Surrey ES, Lietz AK, Schoolcraft WB. Impact of intramural leiomyomata in patients with a normal endometrial cavity on in vitro fertilization-embryo transfer cycle outcome. Fertil Steril. 2001;75:405.
17. Check JH, Choe JK, Lee G, Dietterich C. The effect on IVF outcome of small intramural fi broids not compressing the uterine cavity as determined by a prospective matched control study. Hum Reprod. 2002;17:1244.
18. Oliveira FG, Abdelmassih VG, Diamond MP, Dozortsev D, Melo NR, Abdelmassih R. Impact of subserosal and intramural uterine fibroids that do not distort the endometrial cavity on the outcome of in vitro fertilization-intracytoplasmic sperm injection. Fertil Steril. 2004;81:582.
19. Eldar-Geva T, Meagher S, Healy DL, MacLachlan V, Breheny S, Wood C. Effect of intramural, subserosal, and submucosal uterine fibroids on the outcome of assisted reproductive technology treatment. Fertil Steril. 1998;70:687.
20. Stovall DW, Parrish SB, Van Voorhis BJ, Hahn SJ, Sparks AE, Syrop CH. Uterine leiomyomas reduce the efficacy of assisted reproduction cycles: results of a matched follow-up study. Hum Reprod. 1998;13:192.
21. Casini ML, Rossi F, Agostini R, Unfer V. Effects of the position of fibroids on fertility. Gynecol Endocrinol. 2006;22:106.
22. Bulletti C, Ziegler DE, Levi Setti P, Cicinelli E, Polli V, Stefanetti M. Myomas, pregnancy outcome, and in vitro fertilization. Ann N Y Acad Sci. 2004; 1034:84.
23. Vercellini P, Maddalena S, De Giorgi O, Pesole A, Ferrari L, Crosignani PG. Determinants of reproductive outcome after abdominal myomectomy for infertility. Fertil Steril. 1999;72:109.
24. Fauconnier A, Dubuisson JB, Ancel PY, Chapron C. Prognostic factors of reproductive outcome after myomectomy in infertile patients. Hum Reprod. 2000;15:1751.
25. Barakat EE, Bedaiwy MA, Zimberg S, Nutter B, Nosseir M, Falcone T. Robotic-assisted, laparoscopic,

and abdominal myomectomy: a comparison of surgical outcomes. Obstet Gynecol. 2011;117:256–65.
26. Palomba S, Zupi E, Falbo A, Russo T, Marconi D, Tolino A, et al. A multicenter randomized, controlled study comparing laparoscopic versus minilaparotomic myomectomy: reproductive outcomes. Fertil Steril. 2007;88:933.
27. Holloway RW, Patel SD, Ahmad S. Robotic surgery in gynecology. Scand J Surg. 2009;98:96.
28. Luciano AA. Myomectomy. Clin Obstet Gynecol. 2009;52:362.
29. Muram D, Gillieson M, Walters JH. Myomas of the uterus in pregnancy: ultrasonographic follow-up. Am J Obstet Gynecol. 1980;138:16–9.
30. Karasick S, Lev-Toaff AS, Toaff ME. Imaging of uterine leiomyomas. AJR Am J Roentgenol. 1992;158: 799–805.
31. Marcotte-Bloch C, Novellas S, Buratti MS, Caramella T, Chevallier P, Bruneton JN. Torsion of a uterine leiomyoma: MRI features. Clin Imaging. 2007;31(5):360–2.
32. Neiger R, Sonek JD, Croom CS, Ventolini G. Pregnancy-related changes in the size of uterine leiomyomas. J Reprod Med. 2006;51(9):671–4.
33. Rosati P, Exacoustos C, Mancuso S. Longitudinal evaluation of uterine myoma growth during pregnancy. A sonographic study. J Ultrasound Med. 1992;11(10):511–5.
34. Aharoni A, Reiter A, Golan D, Paltiely Y, Sharf M. Patterns of growth of uterine leiomyomas during pregnancy. A prospective longitudinal study. Br J Obstet Gynaecol. 1988;95(5):510–3.
35. Laughlin SK, Herring AH, Savitz DA, Olshan AF, Fielding JR, Hartmann KE, et al. Pregnancy-related fibroid reduction. Fertil Steril. 2010;94(6):2421–3.
36. De Vivo A, Mancuso A, Giacobbe A, Savasta LM, De Dominici R, Dugo N, Dugo C, Vaiarelli A. Uterine myomas during pregnancy: a longitudinal sonographic study. Ultrasound Obstet Gynecol. 2011;37(3):361–5.
37. Hammoud AO, Asaad R, Berman J, Treadwell MC, Blackwell S, Diamond MP. Volume change of uterine myomas during pregnancy: do myomas really grow? J Minim Invasive Gynecol. 2006;13(5):386–90.
38. Lev-Toaff AS, Coleman BG, Arger PH, Mintz MC, Arenson RL, Toaff ME. Leiomyomas in pregnancy: sonographic study. Radiology. 1987;164(2):375–80.
39. Ouyang DW, Economy KE, Norwitz ER. Obstetric complications of fibroids. Obstet Gynecol Clin North Am. 2006;33(1):153–69.
40. Vollenhoven BJ, Lawrence AS, Healy DL. Uterine fibroids: a clinical review. Br J Obstet Gynaecol. 1990;97:285.
41. Buttram VC, Reiter RC. Uterine leiomyomata: etiology, symptomatology and management. Fertil Steril. 1981;36:433.
42. Li TC, Mortimer R, Cooke ID. Myomectomy: a retrospective study to examine reproductive performance before and after surgery. Hum Reprod. 1999;14: 1735–40.
43. Ramzy AM, Sattar M, Amin Y, Mansour RT, Serour GI, Aboulghar MA. Uterine myomata and outcome of assisted reproduction. Hum Reprod. 1998;13:198.
44. Goldenberg M, Sivan E, Sharabi Z, Bider D, Rabinovici J, Seidman DS. Outcome of hysteroscopic resection of submucous myomas for infertility. Fertil Steril. 1995;64:714.
45. Giatras K, Berkeley AS, Noyes N, Licciardi F, Lolis D, Grifo JA. Fertility after hysteroscopic resection of submucous myomas. J Am Assoc Gynecol Laparosc. 1999;6:155.
46. Varasteh NN, Neuwirth RS, Levin B, Keltz MD. Pregnancy rates after hysteroscopic polypectomy and myomectomy in infertile women. Obstet Gynecol. 1999;94:168.
47. Fernandez H, Sefrioui O, Virelizier C, Gervaise A, Gomel V, Frydman R. Hysteroscopic resection of submucosal myomas in patients with infertility. Hum Reprod. 2001;16:1489.
48. Devi Wold AS, Pham N, Arici A. Anatomic factors in recurrent pregnancy loss. Semin Reprod Med. 2006;24(1):25–32.
49. Qidwai GI, Caughey AB, Jacoby AF. Obstetric outcomes in women with sonographically identified uterine leiomyomata. Obstet Gynecol. 2006;107 (2 Pt 1):376–82.
50. Shavell VI, Thakur M, Sawant A, Kruger ML, Jones TB, Singh M, et al. Adverse obstetric outcomes associated with sonographically identified large uterine fibroids. Fertil Steril. 2012;97(1):107–10.
51. Chen YH, Lin HC, Chen SF, Lin HC. Increased risk of preterm births among women with uterine leiomyoma: a nationwide population-based study. Hum Reprod. 2009;24(12):3049–56.
52. Vergani P, Ghidini A, Strobelt N, Roncaglia N, Locatelli A, Lapinski RH, et al. Do uterine leiomyomas influence pregnancy outcome? Am J Perinatol. 1994;11(5):356–8.
53. Katz VL, Dotters DJ, Droegemueller W. Complications of uterine leiomyomas in pregnancy. Obstet Gynecol. 1989;73:593–6.
54. De Carolis S, Fatigante G, Ferrazzani S, et al. Uterine myomectomy in pregnant women. Fetal Diagn Ther. 2001;16:116–9.
55. Norton ME, Merril J, Cooper BA, et al. Neonatal complications after administration of indomethacin for preterm labor. N Engl J Med. 1993;329:1602–7.
56. Seki H, Takizawa Y, Sodemoto T. Epidural analgesia for painful myomas refractory to medical therapy during pregnancy. Int J Gynaecol Obstet. 2003;83:303–4.
57. Falcone T, Parker WH. Surgical management of leiomyomas for fertility or uterine preservation. Obstet Gynecol. 2013;121:856–68.
58. Burton CA, Grimes DA, March CM. Surgical management of leiomyomata during pregnancy. Obstet Gynecol. 1989;74(5):707–9.
59. Makar AP, Schatteman EA, Vergote IB, Desmedt E. Myomectomy during pregnancy: uncommon case report. Acta Chir Belg. 1989;89(4):212–4.

60. Foissac R, Sautot-Vial N, Birtwisle L, et al. Torsion of a huge pedunculated uterine leiomyoma. Am J Surg. 2011;201(6):e43–5.
61. Leach K, Khatain L, Tocce K. First trimester myomectomy as an alternative to termination of pregnancy in a woman with a symptomatic uterine leiomyoma: a case report. J Med Case Reports. 2011;5(1):571.
62. Ardovino M, Ardovino I, Castaldi MA, Monteverde A, Colacurci N, Cobellis L. Laparoscopic myomectomy of a subserous pedunculated fibroid at 14 weeks of pregnancy: a case report. J Med Case Reports. 2011;5(1):545.
63. Fanfani F, Rossitto C, Fagotti A, Rosati P, Gallotta V, Scambia G. Laparoscopic myomectomy at 25 weeks of pregnancy: case report. J Minim Invasive Gynecol. 2010;17(1):91–3.
64. Pelosi MA, Pelosi 3rd MA, Giblin S. Laparoscopic removal of a 1500-g symptomatic myoma during the second trimester of pregnancy. J Am Assoc Gynecol Laparosc. 1995;2(4):457–62.
65. Son CE, Choi JS, Lee JH, Jeon SW, Bae JW, Seo SS. A case of laparoscopic myomectomy performed during pregnancy for subserosal uterine myoma. J Obstet Gynaecol. 2011;31(2):180–1.
66. Currie A, Bradley E, McEwen M, Al-Shabibi N, Willson PD. Laparoscopic approach to fibroid torsion presenting as an acute abdomen in pregnancy. JSLS. 2013;17(4):665–7.
67. Sentilhes L, Sergent F, Verspyck E, Gravier A, Roman H, Marpeau L. Laparoscopic myomectomy during pregnancy resulting in septic necrosis of the myometrium. BJOG. 2003;110(9):876–8.
68. Walsh CA, Tang T, Walsh SR. Laparoscopic versus open appendectomy in pregnancy: a systematic review. Int J Surg. 2008;6(4):339–44.
69. Devlieger R, Millar LK, Bryant-Greenwood G, Lewi L, Deprest JA. Fetal membrane healing after spontaneous and iatrogenic membrane rupture: a review of current evidence. Am J Obstet Gynecol. 2006;195(6):1512–20.
70. Friedman JD, Ramsey PS, Ramin KD, Berry C. Pneumoamnion and pregnancy loss after second-trimester laparoscopic surgery. Obstet Gynecol. 2002;99(3):512–3.
71. Walsh TM, Borahay MA, Fox KA, Kilic GS. Robotic-assisted, ultrasound-guided abdominal cerclage during pregnancy: overcoming minimally invasive surgery limitations? J Minim Invasive Gynecol. 2013;20(3):398–400.
72. Lee HJ, Norwitz ER, Shaw J. Contemporary management of fibroids in pregnancy. Rev Obstet Gynecol. 2010;3(1):20–7.
73. Lieng M, Istre O, Langebrekke A. Uterine rupture after laparoscopic myomectomy. J Am Assoc Gynecol Laparosc. 2004;11:92.
74. Banas T, Klimek M, Fugiel A, Skotniczny K. Spontaneous uterine rupture at 35 weeks' gestation, 3 years after laparoscopic myomectomy, without signs of fetal distress. J Obstet Gynaecol Res. 2005;31:527.
75. Grande N, Catalano GF, Ferrari S, Marana R. Spontaneous uterine rupture at 27 weeks of pregnancy after laparoscopic myomectomy. J Minim Invasive Gynecol. 2005;12:301.
76. Parker WH, Iacampo K, Long T. Uterine rupture after laparoscopic removal of a pedunculated myoma. J Minim Invasive Gynecol. 2007;14:362.
77. Gyamfi-Bannerman C, Gilbert S, Landon MB, Spong CY, Rouse DJ, Varner MW, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. Risk of uterine rupture and placenta accreta with prior uterine surgery outside of the lower segment. Obstet Gynecol. 2012;120(6):1332–7.
78. Cela V, Freschi L, Simi G, Tana R, Russo N, Artini PG, Pluchino N. Fertility and endocrine outcome after robot-assisted laparoscopic myomectomy (RALM). Gynecol Endocrinol. 2013;29(1):79–82.
79. Kim MS, Uhm YK, Kim JY, Jee BC, Kim YB. Obstetric outcomes after uterine myomectomy: Laparoscopic versus laparotomic approach. Obstet Gynecol Sci. 2013;56(6):375–81.
80. Dubuisso JB, Fauconnier A, Babaki-Fard K, Chapron C. Laparoscopic myomectomy: a current view. Hum Reprod Update. 2000;6(6):588–94.
81. Pitter MC, Gargiulo AR, Bonaventura LM, Lehman JS, Srouji SS. Pregnancy outcomes following robot-assisted myomectomy. Hum Reprod. 2013; 28(1):99–108.
82. Litta P, Conte L, De Marchi F, Saccardi C, Angioni S. Pregnancy outcome after hysteroscopic myomectomy. Gynecol Endocrinol. 2014;30(2):149–52.
83. Roy KK, Singla S, Baruah J, Sharma JB, Kumar S, Singh N. Reproductive outcome following hysteroscopic myomectomy in patients with infertility and recurrent abortions. Arch Gynecol Obstet. 2010; 282(5):553–60.
84. Hassiakos D, Christopoulos P, Vitoratos N, Xarchoulakou E, Vaggos G, Papadias K. Myomectomy during cesarean section: a safe procedure? Ann N Y Acad Sci. 2006;1092:408–13.
85. Kaymak O, Ustunyurt E, Okyay RE, Kalyoncu S, Mollamahmutoglu L. Myomectomy during cesarean section. Int J Gynaecol Obstet. 2005;89(2): 90–3.
86. Kim YS, Choi SD, Bae DH. Risk factors for complications in patients undergoing myomectomy at the time of cesarean section. J Obstet Gynaecol Res. 2010;36(3):550–4.
87. Li H, Du J, Jin L, Shi Z, Liu M. Myomectomy during cesarean section. Acta Obstet Gynecol Scand. 2009;88(2):183–6.
88. Park BJ, Kim YW. Safety of cesarean myomectomy. J Obstet Gynaecol Res. 2009;35(5):906–11.
89. Simsek Y, Celen S, Danisman N, Mollamahmutoglu L. Removal of uterine fibroids during cesarean section: a difficult therapeutic decision. Clin Exp Obstet Gynecol. 2012;39(1):76–8.

90. Song D, Zhang W, Chames MC, Guo J. Myomectomy during cesarean delivery. Int J Gynaecol Obstet. 2013;121(3):208–13.
91. Cesen-Cummings K, Houston KD, Copland JA, et al. Uterine leiomyomas express myometrial contractile-associated proteins involved in pregnancy-related hormone signalling. J Soc Gynecol Investig. 2003;10:11–20.
92. Burbank F. Childbirth and myoma treatment by uterine artery occlusion: do they share a common biology? J Am Assoc Gynecol Laparosc. 2004;11:138–52.
93. Walker CL, Cesen-Cummings K, Houle C, et al. Protective effect of pregnancy for development of uterine leiomyoma. Carcinogenesis. 2001;22:2049–52.
94. Yang JH, Chen MJ, Chen CD, Chen SU, Ho HN, Yang YS. Optimal waiting period for subsequent fertility treatment after various hysteroscopic surgeries. Fertil Steril. 2013;99(7):2092–6.
95. Chang WC, Chang DY, Huang SC, et al. Use of three-dimensional ultrasonography in the evaluation of uterine perfusion and healing after laparoscopic myomectomy. Fertil Steril. 2009;92:1110–5.
96. Darwish AM, Nasr AM, El-Nashar DA, et al. Evaluation of postmyomectomy uterine scar. J Clin Ultrasound. 2005;33:181–6.
97. Seinera P, Gaglioti P, Volpi E, et al. Ultrasound evaluation of uterine wound healing following laparoscopic myomectomy: preliminary results. Hum Reprod. 1999;14:2460–3.
98. Kumakiri J, Kikuchi I, Kitade M, et al. Evaluation of factors contributing to uterine scar formation after laparoscopic myomectomy. Acta Obstet Gynecol Scand. 2010;89:1078–83.

Cesarean Myomectomy

16

Antonio Malvasi, Michael Stark, and Andrea Tinelli

Introduction

Uterine fibroids or myomas are the most common pelvic tumors in women. Their occurrence in the reproductive age group is 25–40 % [1].

Uterine myomas are observed these days more frequently in pregnancy with an estimated incidence of 2–4 %, because many women are delaying childbearing until their late thirties or the beginning of their forties, the time of greatest risk for myoma growth [2, 3]. Uterine myomas are commonly encountered in women older than 30 years [1, 2] and their growth is directly related to exposure to the circulating estrogens levels. The prevalence of leiomyomas among pregnant women ranges from 0.1 to 3.9 % [4–8]. The effective rate of uterine myomas in pregnancy is unknown; however, they are associated with numerous pregnancy-related maternal and fetal complications like spontaneous abortion, preterm labor, placental abruption, post partum hemorrhage and high rate of cesarean deliveries [3, 9].

Complications in pregnancy, labor and delivery occur almost twice as frequently among women diagnosed with uterine myomas than in those without [4–7]. The literature suggests a high rate of cesarean deliveries in women with myomas up to 39. 95 % [10].

In fact, in a population-based series of women who delivered singleton, live infants in Washington, Coronado et al. [10] observed from 1987 to 1993 an independent association between uterine leiomyomas and abruptio placentae, fetal malpresentation, dysfunctional labor and breech presentation. The authors found an increased risk of 58 % for cesarean section among 2,065 women with uterine myomas, compared to 17 % in 4,243 women without myomas (odds ratio [OR] 6.39, 95 % CI 5.46–7.5). Some of the excess risk may be related to incidental detection of myomas during cesarean section. Conversely, the aforementioned complications of abruption, dysfunctional labor and breech presentation are usually managed by cesarean section, indicating that the increased risk is probably related to the leiomyomas themselves.

A. Malvasi, MD (✉)
Obstetric and Gynecology,
Santa Maria Hospital, Bari, Italy

International Translational Medicine and
Biomodelling Research Group,
Department of Applied Mathematics,
Moscow Institute of Physics and Technology
(State University), Moscow Region, Russia
e-mail: antoniomalvasi@gmail.com

M. Stark
New European Surgical Academy (NESA),
Berlin, Germany
e-mail: mstark@nesacademy.org

A. Tinelli, MD
Gynecology and Obstetric, Vito Fazzi Hospital,
Lecce, Italy

International Translational Medicine and
Biomodelling Research Group,
Department of Applied Mathematics,
Moscow Institute of Physics and Technology
(State University), Moscow Region, Russia
e-mail: andreatinelli@gmail.com

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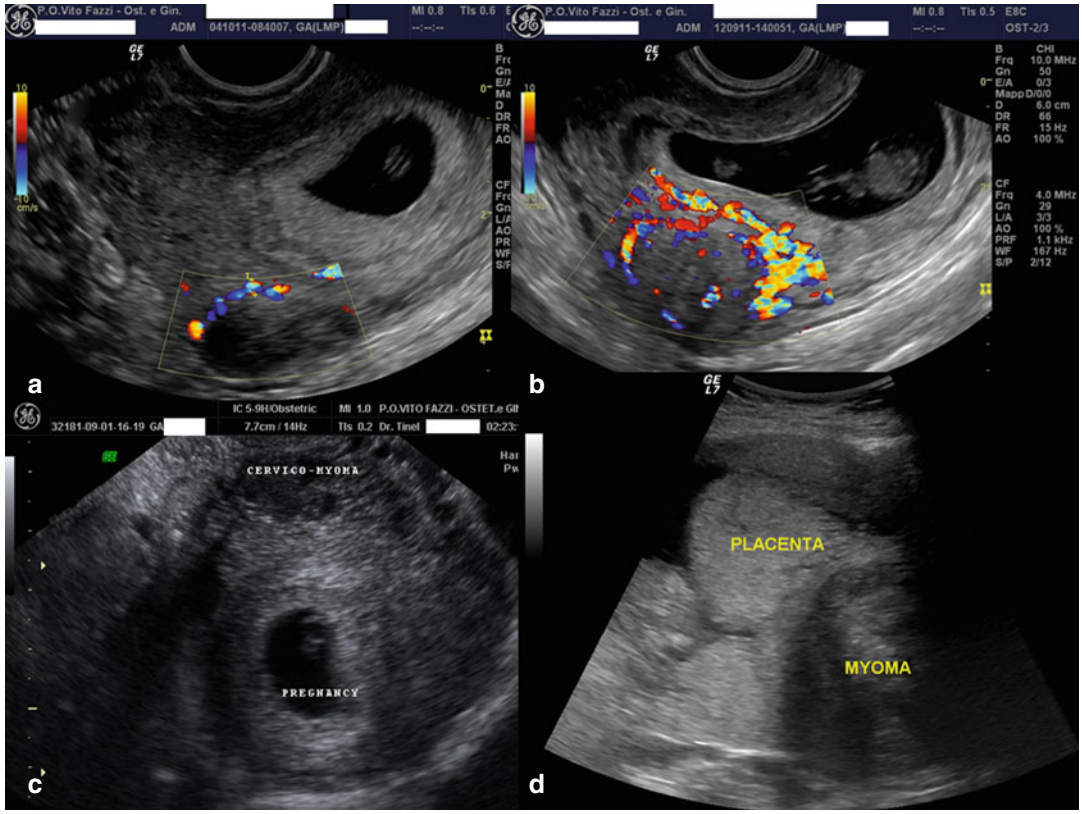

Fig. 16.1 Ultrasonographic scan of myomas during pregnancy: (**a**) a subserous myoma of 2 cm in a pregnant at 5 weeks of pregnancy, with the eco Doppler enhancing peripheral myoma vascularization; (**b**) a posterior intramural corporal myoma of 3 cm of diameter at 8 weeks of pregnancy, with the eco Doppler enhancing placental and peripheral myoma vascularization; (**c**) an anterior cervical myoma in patient at 6 weeks of pregnancy; (**d**) a large myoma previo of 9 cm of diameter, at 18 weeks of pregnancy

And, if cesarean delivery is the worldwide most common obstetric operation [11], it is mandatory to consider the possibility of being faced with the necessity of having to remove, necessarily and properly, a myoma during cesarean section or, in other cases, to deliver by repeat cesarean delivery in case of a previous myomectomy.

Consequences of Myomas in Pregnancy

The medical literature has reported an increasing rate of myomectomies during cesarean section in the past decade, probably due either to the extensive use of ultrasonography that has improved diagnostic capability of detecting myomas in pregnancy [12] (Fig. 16.1), or myomectomy during cesarean delivery is not an almost life threatening surgery as it was considered to be before [2, 9–12]. Therefore, it is mandatory to use ultrasonography routinely to detect either fetal wellbeing or the growth of diagnosed myomas in pregnancy. Myomas can be asymptomatic or associated with serious complications and the overall risk of major complications arrives up to 71 %, combining pregnancy, delivery and puerperium [2, 4].

Less common complication of myoma in pregnancy are disseminated intravascular coagulopathy, cervical pregnancy, spontaneous hemoperitoneum, uterine inversion, uterine torsion, urinary retention in the first trimester; about fetal complications related to myoma in pregnancy, the literature showed limb reduction anomalies and head and body deformities related to fetal compression [1, 3, 6–8, 10, 13].

Operations on the uterus during the CS, except for excision of pedunculated myomas (Figs. 16.2 and 16.3), are traditionally discouraged for the aforementioned reasons, as uncontrolled and profuse bleeding, that may lead to a severe anemia, puerperal infection and to hysterectomy.

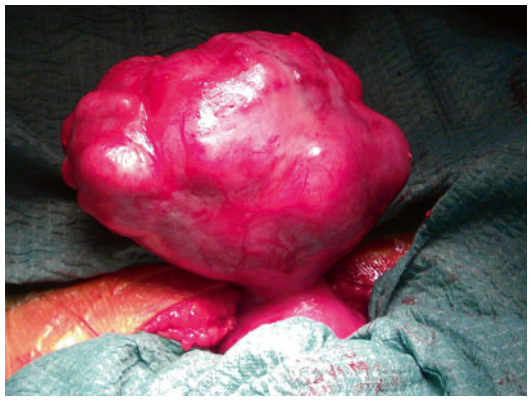

Fig. 16.2 A large fundal pedunculated myoma in pregnancy of 10 cm of diameter, to be removed during cesarean section

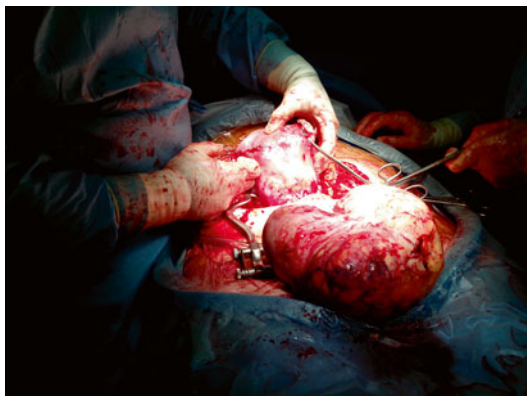

Fig. 16.3 A lateral giant fundal pedunculated myoma in pregnancy of 22 cm of diameter, removed during cesarean section

Uterine fibroids, a part the risk of spontaneous abortion, preterm labor, placental abruption and post partum hemorrhage, have been associated with a 10–40 % obstetric complication rate premature labor and adverse obstetric outcomes during and after delivery [3, 5, 6, 10, 13, 14].

The greatest risks of cesarean myomectomy frequently results from lack of knowledge of the presence of uterine myoma during unexpected or scheduled CS, or from a wrong knowledge of myoma location. Myomas lead to dystocia as tumor previa (Fig. 16.4) or, when located in the lower uterine segment (LUS), they cause extreme technical difficulties during closure of the hysterotomy when leaving the fibroid *in situ*.

Also for the above reasons, myomectomy performed during pregnancy still remains a high-risk operation.

Later on, with the accumulated experience and lack of major complications coupled with the fact that no evidence-based contraindications could be found in the literature, we were inspired to develop our own technique with our research group, and to use it also for large fibroids that were located away from the LUS.

The only absolute contraindication for cesarean myomectomy stated in the literature is intrasurgical uterine hypotony/atony, following the delivery of the fetus [15–19].

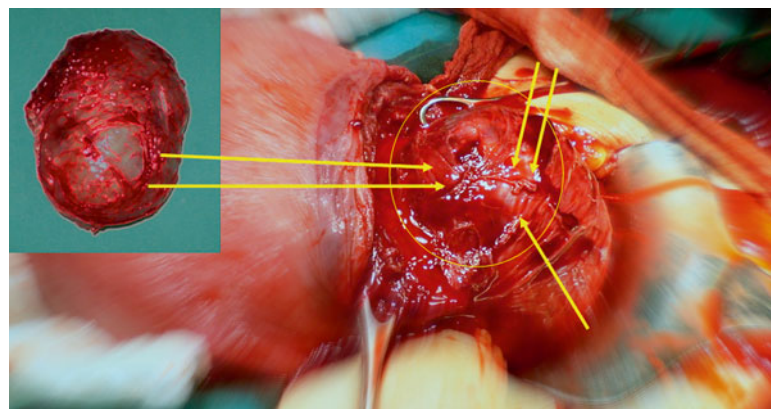

Fig. 16.4 A tumor previa in pregnancy of 8 cm of diameter, located on lower uterine segment; surgeons performed the hysterotomy on the top of myoma, removed fetus and proceed to enucleate myoma previa (in the *box* in the *upper left*)

Uterine Modified Anatomy and Physiology with Myomas in Pregnancy

Pregnancy induces profound anatomical and physiological changes to uterus and its vascularization, all factors to consider before starting an operation during pregnancy. So, once diagnosis of myoma is confirmed by ultrasonography, management of myoma encountered during CS poses a therapeutic dilemma: how myomas should be better managed during pregnancy, labor or delivery? For example in case of myomas located next to the LUS. In such cases, and in order to deliver the baby, the obstetrician is faced with the emergency decision of making the incision through or near the myoma, removing it, or choosing the classical longitudinal incision to deliver the baby while avoiding cutting through or near the myoma.

The surgeon has to make decisions if myomectomy is really indicated during cesarean delivery or it should be delayed for some months after delivery.

During pregnancy, uterine enlargement involves marked hypertrophy of the muscle cells and a progressive increase in the uteroplacental blood flow ranging from approximately 450–650 mL/min near term [20, 21].

This increased blood flow is mediated primarily by means of vasodilatation. The uterine arteries' diameter doubles by 20 weeks of gestation and concomitant mean Doppler velocimetry is increased eightfold [22].

Thus, any surgical procedure performed on or around the uterus has the potential of causing severe hemorrhage and, for this reason, uterine myomectomy during cesarean section has consistently been discouraged, in the past years, as a high-risk procedure.

In cases of a small pedunculated subserous fibroid attached to the uterus with a small pedicle, myomectomy is relatively easy, with clamping, cutting and suturing of the myoma pedicle.

On the contrary, resection of an intramural myoma is inadvisable and contraindicated during cesarean section by some obstetric textbooks [23, 24], due to the risk of profuse uncontrolled bleeding that could lead to hysterectomy. In such books, the authors remark that myomas often undergo a remarkable involution after delivery and they may even become pedunculated, making myomectomy (if necessary) easier and safer as a postpartum intervention than at the time of cesarean section [24, 25].

Furthermore, because of bizarre nuclear changes at pathologists examination, myomas enucleated during pregnancy or delivery can be often interpreted as leiomyosarcoma, thus leading to unnecessary anxiety and fear. In the scientific literature there are also several data and lately larger studies indicating myomectomy during CS or even during pregnancy as a probably safer procedure than previously believed.

Literature on Cesarean Myomectomy

In 1989, Burton et al. [7] were probably the first to report the procedure of a myomectomy during pregnancy and cesarean section (CS). They reviewed an 8-year experience with surgical management of leiomyomata during pregnancy at the Los Angeles County Women's Hospital. Five women underwent explorative laparotomy only, six had a myomectomy during pregnancy, and three had a hysterectomy; one patient aborted after surgery. Thirteen other women had incidental myomectomies at cesarean delivery; one of these had an intraoperative hemorrhage. No other complications were reported.

During 1997–2001, Ben Rafael et al. [26] evaluated prospectively the surgical outcome of a planned myomectomy during CS in cases where the fibroids were either known to be large enough to require surgery at a later stage, or when the fibroid led to malpresentations. The outcome investigated parameters were: type of anesthesia, type of incision, intraoperative blood loss, need for blood transfusion, intra- or postoperative complications, and length of hospital stay. Thirty-nine myomas were removed from 32 patients in 15 elective and 17 emergency procedures. Indications for CS were obstetrical (breech presentation, more than one previous CS, among

others) in most cases. The indications in the other women were: myomas causing dystocia as tumor previa, fibroid degeneration and intractable pain, and uterine cavity penetration in cases of previous myomectomies. Ninety percent of the myomas were subserous or intramural, and 10 % submucous. The average size (largest dimension) was 6 cm (1.5–20), with 26 myomas measuring >3 cm, and 11>6 cm. Four CS (12.5 %) were classical, and the rest low-segmental. Most of the operations were performed under regional anesthesia (spinal block). The difference in hemoglobin and hematocrit levels before and 12 h after the operation was significantly lower in patients who underwent cesarean myomectomies, compared to those who underwent CS avoiding myomectomy ($p<0.05$), yet only four patients required a blood transfusion. Two patients underwent repeated surgeries: one with two large myomas and excessive bleeding, and the other due to a subcutaneous hematoma. No hysterectomy was required. Six patients had postpartum fever (18.7 %). The average duration of hospitalization was 5.7 days, with five patients requiring more than 6 days of hospitalization. There was no correlation between complications or duration of hospital stay and patient age, gravidity, parity or indication for CS [26].

Michalas et al. [27] performed a myomectomy on a 31-year-old primigravida during the 15th week of pregnancy due to a large, 23 cm diameter myoma. At the 39th week of pregnancy, during the CS, eight fibroids obstructing the lower part of the uterus were removed. There were no maternal or fetal complications.

Çelik et al. [28], in his study conclusions, reported that myomectomy could be also safe if performed during pregnancy. Five pregnant women with myomas requiring surgical removal because of severe pain underwent a myomectomy at a median gestational age of 17.8 ± 3.4 weeks. The mean size of the myomas was 14.0 ± 3.8 cm. No major surgical and postoperative complications were observed and all the pregnancies continued to term.

Reporting surgical experiences of the last century, other authors reported their experience with cesarean myomectomies, as Hsieh et al. [29] who retrospectively reviewed 47 incidental cesarean myomectomies. The procedure added only 11 min to the operating time, 112 mL to the operative blood loss, and extended the hospital stay by about 1.5 days. There was no wound infection or serious morbidity.

Dimitrov et al. [30] conducted a prospective study in Bulgaria to evaluate myomectomy during CS as "a routine method". Their study group comprised of 21 cases that underwent myomectomies during CS, and were compared to a control group of 162 consecutive CS without having undergone myomectomies. They found that myomectomy during CS increased the blood loss by 10 %. Analysis of the cases with severe hemorrhage showed that they were related to other placental disorders (abruptio placentae and placenta previa) as the main cause of the increased blood loss. There were no postoperative complications.

Omar et al. [31] reported two cases with large, uterine myomas, situated in the anterior aspect of the lower segment, complicating pregnancy at term. A myomectomy in both instances facilitated delivery of the fetus through the lower segment, enabling vaginal delivery in subsequent pregnancies.

Brown et al. [15] from Jamaica retrospectively analyzed the records of 32 women: 16 underwent cesarean myomectomy and were compared to 16 cases of CS chosen as the first normal CS occurring after each cesarean myomectomy. The myomectomy was always performed after delivery of the fetus and after the administration of oxytocin. Diluted oxytocin was also injected into the myoma's capsule to facilitate hemostasis. The results indicated that the patients who underwent a cesarean myomectomy were significantly older ($p<0.0001$), but there was no statistical difference in parity between the two groups. The median number of myomas found was two (range: 1–6). The mean blood loss was similar among the two groups: 403 ± 196 ml in the myomectomy group vs. 356 ± 173 ml in the regular CS. No significant difference between the groups was observed in relation to hemoglobin levels, need for blood transfusion, febrile morbidity or the length of hospital stay.

Ehigiegba et al. [16] prospectively assessed the intra- and post-operative complications of cesarean myomectomies in 25 pregnancies. Patients with known fibroids were required to provide their consent for a possible cesarean myomectomy. Leiomyomas in the anterior uterine wall (cervical, body or fundal) were removed through the CS incision when possible, otherwise other incision(s) were performed. Nineteen patients (76 %) underwent emergency CS after trial of labor, while 6 (24 %) had elective CS. A total of 84 fibroids were removed. In most women there were only 1–2 leiomyomas, but in 1 patient 22 myomas (!) were removed; 57 % of the myomas were intramural, 35.7 % subserous of which only 1 % was pedunculated. Anemia was apparent in 60 % of patients but only five patients (20 %) required blood transfusion. No single hysterectomy was indicated. Three patients (12 %) had subsequent pregnancies, two of whom had normal vaginal deliveries and one underwent a repeat CS.

The largest report by Roman and Tabsh [32] compared the results of caesarean myomectomies to "no touch" CS. They retrospectively evaluated 111 women who underwent a cesarean myomectomy and 257 women with documented fibroids who underwent CS alone. The two groups were similar with respect to median age, median parity, median gestational age and median size of the fibroids. Most patients in both groups underwent low transverse incision CS. In 86 % of the patients the fibroids were incidental findings, while in the rest symptoms such as pain, dystocia and unusual appearance of the myoma dictated its removal. The incidence of hemorrhage in the study group was 12.6 %, compared with 12.8 % in the control group ($p=0.95$). There were no statistically significant increases in the incidence of postpartum fever, operating time, and length of postpartum stay. The size of the fibroid did not appear to affect the incidence of hemorrhage. After stratifying the procedures by type of fibroid removed, intramural myomectomy was found to be associated with a 21.2 % incidence of hemorrhage, compared with 12.8 % in the control group, but this difference was not statistically significant ($p=0.08$). No patient in either group required hysterectomy or embolization following the operation. A similar study by Kaymak et al. [33] on 40 patients undergoing a cesarean myomectomy compared to 80 patients with untouched myomas during CS also showed that performing a myomectomy during CS does not increase the surgical and postoperative complication rate.

Although all the above mentioned studies and reports indicate a good outcome after a cesarean myomectomy, or even after performing a myomectomy during pregnancy, one should remember that hemorrhage can still occur and lead to severe consequences.

Literature showed even a case of maternal death following cesarean myomectomy, caused by massive hemorrhage and subsequent coagulopathy by Disseminated Intravascular Coagulation [34].

Recently authors suggested the use of intraoperative blood salvage in pregnants with planned cesarean myomectomy, particularly when massive intraoperative hemorrhage is expected [35]. These authors presented a preliminary experience with intraoperative blood salvage during cesarean section in four patients with fibroids, two of which scheduled for cesarean myomectomy. The volume of salvaged blood was 450 and 700 ml, respectively. The authors did not encountered any complications caused by blood salvage itself.

Exacoustos et al. [5] reported nine myomectomies performed during cesarean delivery. Of these, three were complicated by severe hemorrhage, indicating hysterectomy. The authors emphasized the role of various ultrasound findings in identifying women at risk for myoma-related complications: the size of the myoma, its position, location, relationship to the placenta, and echogenic structure.

Several recent studies have described techniques that can minimize blood loss at cesarean myomectomy, including uterine tourniquet [36] bilateral uterine artery ligation [37] and the use of electrocautery [38].

Serious issue regarding use of those techniques is long duration of surgery, which was 89 ± 41 min in the study of Desai et al. [39], who used uterine and ovarian artery ligation. Such a

prolonged surgery can be a significant cause of postopeartive morbidity, thus influencing overall cesarean myomectomy complication rate.

However, the majority of the mentioned publications concludes that a myomectomy performed at the time of CS should not increase the risk of hemorrhage and postoperative fever and should not prolong hospital stay. In fact, cesarean myomectomy was stated as a feasible and safe procedure when performed by an experienced surgeon [15, 16, 32, 33].

Pedunculated subserous myomas can be safely removed even if of large size.

Subserous and intramural myomas that are located at the LUS can and probably should be removed and not bypassed by performing a classical incision.

Performing an elective myomectomy from other uterine locations should be considered with caution, since in most of these myomas involution will occur to an insignificant size during puerperium. Meticulous attention to hemostasis, enucleation using sharp dissection with Metzenbaum scissors, adequate approximation of the myometrium and all dead spaces to prevent hematoma formation can increase the safety of the procedure. Despite the lack of prospective and randomized studies, the retrospective investigations clearly show that the tradition that discouraged caesarean myomectomy should be reassessed. Women with known myomas undergoing elective or emergency CS should be properly informed in order to obtain their consent for the option of performing a cesarean myomectomy.

Traditional Technique of Cesarean Myomectomy

The operation should be performed, at least at the outset, by a gynecologist who is proficient in myomectomies on non-gravid uteri [40]. After delivery, the hysterotomy enables the maximal myoma exposure for its removal and the minimal myometrial damage for hysterorrhaphy. Myomectomies could be performed through a transversal or vertical incision, depending on the attitude and preferences of surgeon.

In case on myomas located near the hysterotomy, an interlocked suture is temporarily placed on the edge of the cesarean uterine incision without closure. In such cases, myomectomies are preferably performed from the edge of the cesarean section incision (for myomas located near lower uterine segment). This also facilitates working from within the uterine cavity or from the outer part of the uterus without significant bleeding from the hysterotomy. In case of fibroids located far from cesarean section incision, myomectomies are preferably performed by making a new incision above the myoma in instances where they are located in a site remote from the CS incision.

Surgeons always perform the myoma dissection from myometrium using a sharp Metzenbaum scissor. Intravenous oxytocin drip is generally given after enucleation of the fibroid (some surgeons prefer also during myomectomy). No tourniquet is used by many surgeons as routine; however this may be used to control an unexpected bleeding. Suturing of the fibroid base is traditionally performed by using two layers of interrupted sutures and a baseball-type suture is used for the serosa as a third layer [40, 41].

One important issue with myomectomy is controlling blood loss from the raw myoma beds after their removal. Blood loss is generally estimated from the suction aspiration, and from weighing swabs and drapes used during surgery. Several techniques to reduce blood loss have been studied and reported.

A randomized trial comparing vasopressin and saline injected into the serosa prior to the uterine incision showed that vasopressin is extremely effective for decreasing blood loss. In this study, 50 % of patients receiving saline required transfusion, while none of those in the vasopressin group required transfusion (13 % vs 5 % decrease in hematocrit values) [42].

To reduce bleeding after caesarean myomectomy some surgeons sometimes place tourniquets around the uterus. This is usually performed, especially for in case of placenta accreta [43, 44], by perforating a window in the broad ligament at the level of the internal cervical os bilaterally and passing a Foley catheter or red rubber catheter

through the perforated windows and around the cervix and then tightening it with a clamp to constrict the uterine vessels. In combination with this, vascular clamps are generally placed on the utero-ovarian ligaments [45].

Two randomized trials compared vasopressin and tourniquet use after myomectomy.

In 1996, Fletcher et al. showed that vasopressin was associated with less blood loss and lower risk of either transfusion or blood loss of more than 1 L [46].

In 1993, Ginsberg et al. [47] noted no statistically significant difference between the groups, although their study was much smaller. No studies are available comparing tourniquet use with any tourniquet use. Study results very clearly suggest that vasopressin (usually 20 U in 50–100 mL normal saline) should be injected routinely prior to making the incision in the wall of the uterus. Whether additional use of a tourniquet decreases blood loss remains unclear. After dilute vasopressin has been injected, an incision is made through the wall of the uterus into the myoma. Once the plane between the myometrium and myoma has been defined, it is dissected bluntly and sharply until the entire fibroid is removed. As many fibroids as possible are removed through a single incision. Once the fibroids have been removed, the defect is closed in layers with delayed absorbable suture [47].

Proper placement of the incision side is frequently overlooked but is important.

In 1993, Tulandi et al. [48] studied 26 women with uteri larger than 6–8 weeks' size. Abdominal myomectomies were performed, followed by a second-look laparoscopy 6 weeks later. Patients with incisions in the posterior wall of the uterus had a much higher likelihood of significant adhesions as measured by percentage with adhesions or American Fertility Society (AFS) adhesion score compared with patients with incisions in the fundus or anterior wall of the uterus [48].

Investigations of Cobellis et al. on scar healing at myomectomy site following cesarean section, by clinical and ultrasound investigations [49, 50], concluded that a possible cause for such observation could be the activation of immune system in pregnancy. Similar results are also suggested by Lee et al. [51], while other researchers suggested that better quality of uterine scar in such cases should enable a safe subsequent vaginal delivery, and makes scar less prone to uterine rupture [52]. Further, during surgery, surgeons need to change the hysterotomic incision. According to a study on this topic, T incision in the uterus is necessary in 0.8 % of CS in the general population [53], and this occur as a consequence of fibroids' location on at term uterus, which requires the surgeon to change strategy of surgical steps.

One of the main indications for corporal cesarean section in literature are fibroids [54, 55]. Localization and the size of the fibroids may represent an indication for corporal cesarean section, as well documented [56–58]. Although some authors suggest cesarean myomectomy prior to the delivery of the fetus, as a method to avoid corporal cesarean section, there are cases of corporal cesarean section due to expansion of the hysterotomic incision for the fibroids' location [59]. Investigations on cesarean myomectomy already published [55–62] does not provide the incidence of either uterine corporal or T incisions, although there are some studies and case reports describing their use, even if without sample size details.

About corporal cesarean section, Roman and Tabsh [32] reported 13 patients on 368 women with fibroids (3.53 %) delivered by corporal cesarean section, while Simsek et al. [63] have recorded on 70 patients 2 cases (2.86 %) of corporal cesarean section, and Ben Rafael et al. [26] had only 4 of 32 (12.5 %).

In some cases, cesarean myomectomy is mandatory for delivery of the fetus. Sparić et al. [59] described a case of cesarean myomectomy not decisive for fetal extraction, so the hysterotomy was needed to be expanded into a inverted T incision, even if the fetal extraction was possible only by fetal version in a pregnant with multiple fibroids. It's also important to remember that difficulties in fetal extraction can cause iatrogenic fetal injuries, as described by Adesiyn et al. [64]. These authors reported a neonate with fracture of humerus and clavicular bone during delivery, out of 22 pregnants in their study.

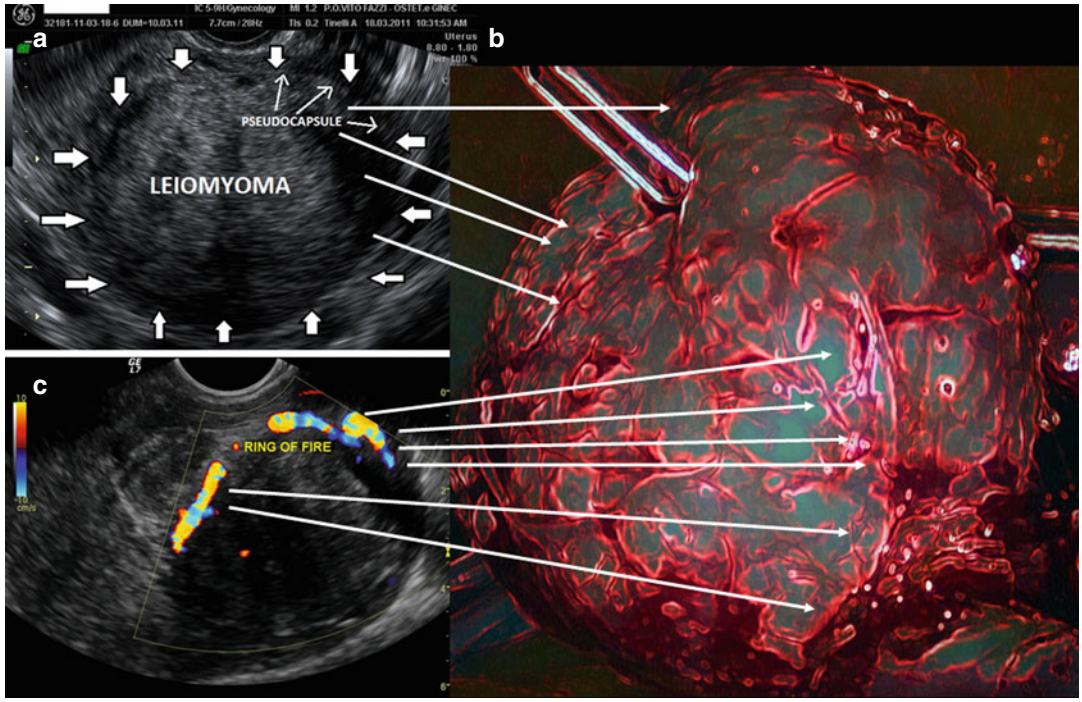

Fig. 16.5 Ultrasonographic scan of myomas and its pseudocapsule; (**a**) in the *top on the left*, the pseudocapsule highlighted by *arrows*; (**b**) in the *lower left*, the echo Doppler shows the pseudocapsule surrounding myoma, appearing as a "ring of fire"; (**c**) to the right, the myoma image covered by fibroneurovascular network

Intracapsular Cesarean Myomectomy

Myoma pseudocapsule is a neurovascular bundle or fibrovascular network attached to the fibroids, which separates the fibroids from the normal myometrium. At ultrasonographic exam, myoma pseudocapsule appears as a white ring around fibroid, and at echo Doppler check, it appears as a "ring of fire", even in pregnancy (Fig. 16.5).

It has been shown that the pseudocapsule not only has similar architecture to the normal myometrium but also contains different neurofibers and neuropeptides (Fig. 16.6). Consequently, a pseudocapsule damage during myomectomy surely negatively impact successive on myometrial healing, although a variety of factors may affect the postoperative healing. Therefore, the excision of a fibroid in daily clinical practice should be done inside the pseudocapsule separating this vascular network [65, 66], even during myoma previa enucleating during cesarean delivery (Figs. 16.7 and 16.8).

After the development of a well detailed technique, the intracapsular myomectomy, successfully performed during laparoscopy in non pregnant women with single or multiple fibroids [67, 68], the authors decided to study their methods of myomas removal during CS, exploring its outcomes.

During the years 2005–2011, our international research group [69] prospectively evaluated the surgical outcome of intracapsular myomectomy during CS, in University affiliated Hospitals, by a prospective case–control study on 68 patients who underwent intracapsular cesarean myomectomy, compared with a control group of 72 patients with myomatosic pregnant uterus who underwent cesarean section without myomectomy.

All operations were ever performed by gynecologists proficient in intracapsular myomectomies on non-gravid uteri, and by CS by Stark's method, under regional anesthesia.

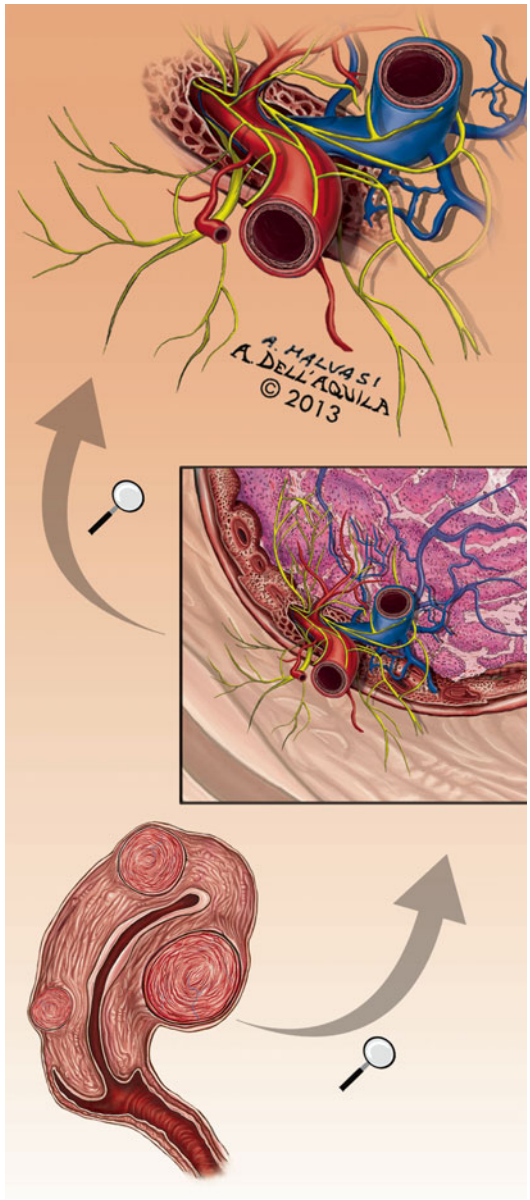

Fig. 16.6 Myoma pseudocapsule is a dense fibroneurovascular pseudocapsule surrounding fibroid (at the *centre of figure*), rich of neurotrasmitters and growth factors (*on the top*), with a proper angiogenic profile that covers all uterine myomas (*bottom image*)

A routine intracapsular cesarean myomectomy was then done for all anterior fibroids (Fig. 16.9): cervical, body, or fundal, using the same cesarean incision where possible, or utilizing other incisions, when necessary.

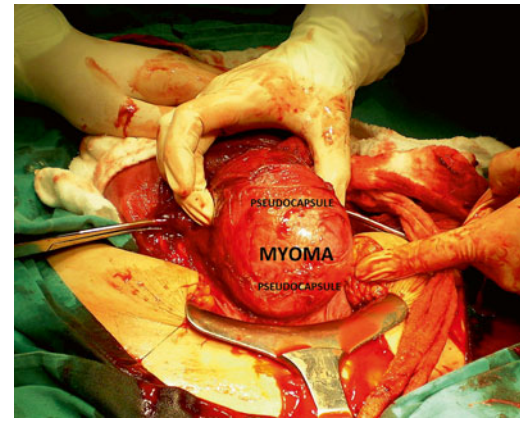

Fig. 16.7 The image represents the enucleation of a myoma during a prior cesarean section, after the birth of newborn; the pseudocapsule covering the myoma is clearly visible during myomectomy

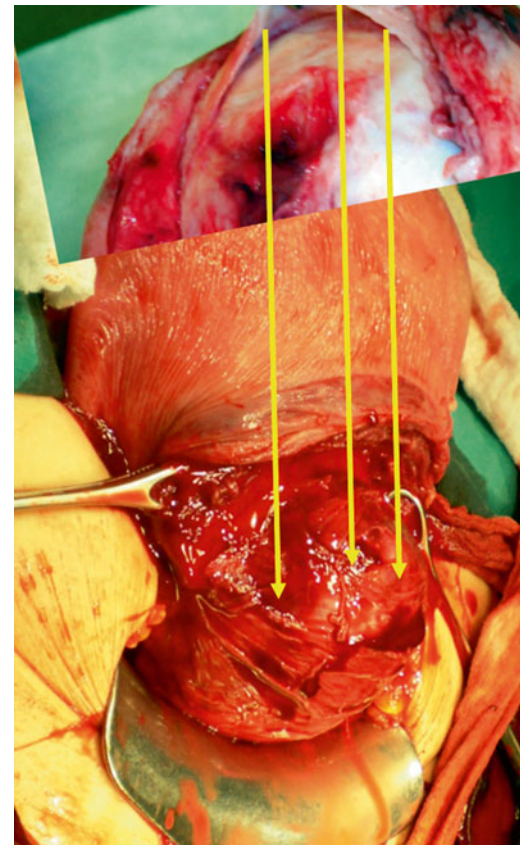

Fig. 16.8 The image expresses the pseudocapsule magnificence during lower uterine segment myomectomy; at the top, it is clearly visible the pseudocapsule separated from the myoma

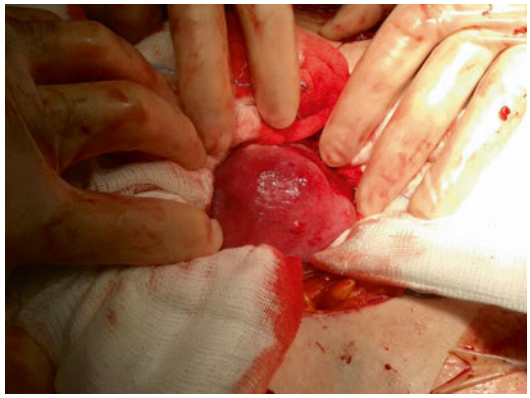

Fig. 16.9 An anterior fibroid to enucleate during cesarean section

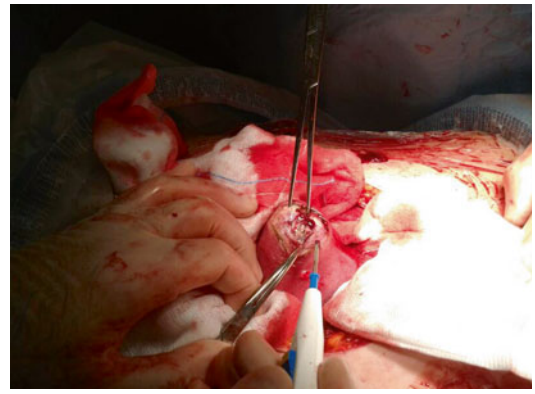

Fig. 16.12 During the cesarean myomectomy, the surface of the myoma is reached and its fiber bridges separated from tumor by monopolar electric scalpel

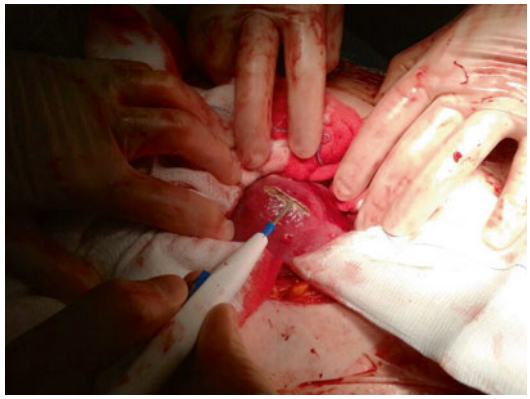

Fig. 16.10 A linear incision is made over the uterine serosa direct to myoma by a monopolar electro-scalpel

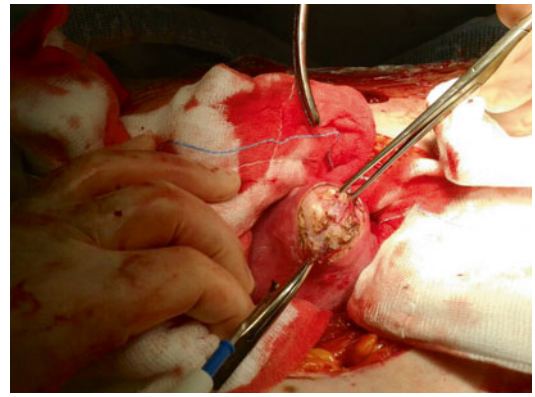

Fig. 16.13 Myoma is gently hooked and carefully extracted from its capsule, during myomectomy

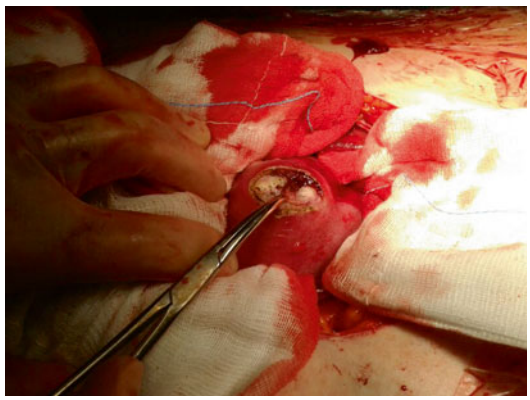

Fig. 16.11 Surgeon gradually proceeds in the dissection of the myoma from the myometrium until opening the pseudocapsule, enabling to enter the relatively bloodless plan between the pseudocapsule and its myoma

Each intracapsular cesarean myomectomy was performed after LUS closure. A linear incision was made over the uterine serosa direct to myoma by a scalpel or a monopolar electroscalpel (Fig. 16.10) at low voltage (≤30 W), gradually until opening the pseudocapsule, enabling to enter the relatively bloodless plan between the pseudocapsule and its myoma (Fig. 16.11).

Once the surface of the myoma was reached and its fiber bridges separated (Fig. 16.12), the myoma was hooked and extracted from its capsule (Fig. 16.13), also by traction and pushing down the capsule using a sharp Metzenbaum scissors. The hemostasis during intracapsular cesarean myomectomy was always reached by

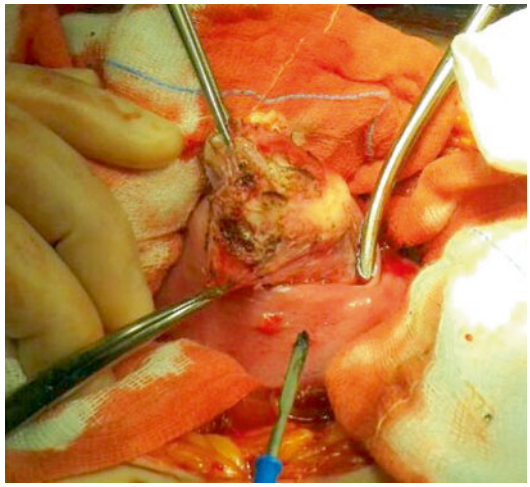

Fig. 16.14 The hemostasis during intracapsular cesarean myomectomy is always reached by gentle low voltage coagulation (≤30 W) of pseudocapsule vessels, with minimal small bleeding

gentle low voltage coagulation (≤30 W) of pseudocapsule vessels (Fig. 16.14), with minimal blood loss. Generally, 10 I.U. of intravenous oxytocin drip was given as a standard to all patients to control bleeding, after enucleating of the fibroid. For myomas located near LUS, we temporarily changed operation' steps: after completion of the CS, an interlocked suture is temporarily placed on the edge of the cesarean uterine incision without closure. Then we performed intracapsular cesarean myomectomies from the edge of the cesarean incision. This also facilitates working from within the uterine cavity or from the outer part of the uterus without significant bleeding from the CS incision. After that, in case of other myomas far from LUS, surgeons made a new incision above the myoma in instances where they were located in a site remote from the CS incision.

Suturing of the fibroid base (Fig. 16.15) was routinely performed by using two layers of interrupted absorbable sutures (1-0 caliber vicryl) and a baseball-type suture was used for the serosa, using a continuous absorbable suture (2-0 or 3-0 caliber vicryl), as a third layer (Fig. 16.16). Pelvic irrigation was done with saline solution. Post-operatively, the oxytocin infusion was continued for 12–24 h in parallel with normal saline infusion.

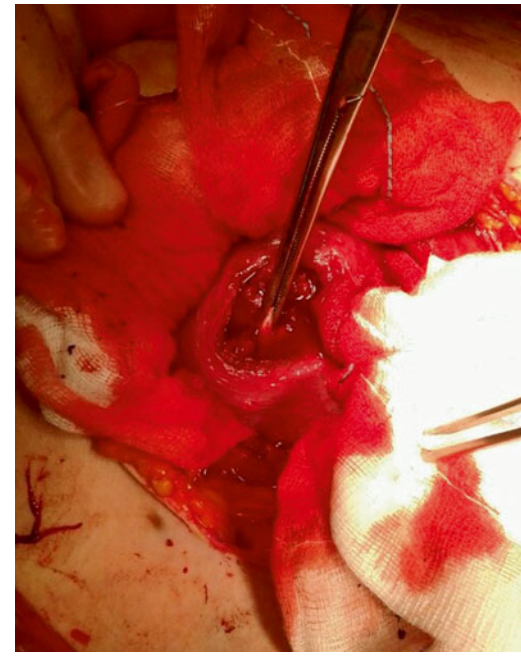

Fig. 16.15 The fibroid base enhancing by a surgical clamp

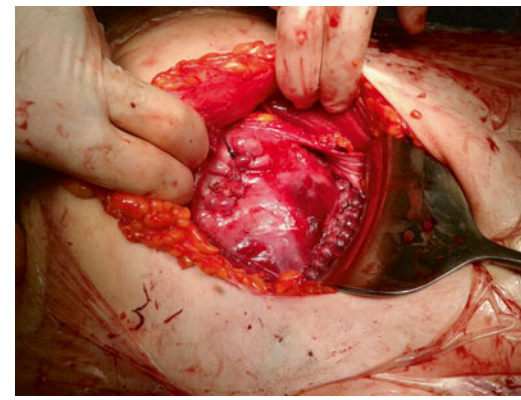

Fig. 16.16 The final result of uterine suturing after cesarean intracapsular myomectomy

Seventy-two control subjects were randomly selected among pregnant women with myomas undergoing CS without myomectomy, at the same Institutions and during the same period, and CS' indications were: breech presentation, more than one previous CS, CS on demand. These women did not receive cesarean myomectomy since they refuse this operations and both myomectomy and control groups were similar in terms of characteristics without any statistical differences.

Table 16.1 Blood tests and outcome differences among intracapsular cesarean myomectomy (ICM) and cesarean sections, as control group

	Cesarean myomectomy (CM) 68 patients	Control group (CS) 72 patients	*P* value
Pre-operative hemoglobin values (g/dl) (mean ± S.D.)	12.1 ± 1.5	11.8 ± 1.3	NS
Post-operative hemoglobin values (g/dl) (mean ± S.D.)	10.6 ± 1.8	10.2 ± 1.4	NS
Mean change in hemoglobin values (g/dl)	1.5 ± 0.3	1.6 ± 0.1	NS
Incidence of intraoperative hemorrhage (>1 L of blood)	3 (4.4 %)	4 (5.5 %)	NS
Frequency of blood transfusion	4 (5.8 %)	4 (5.5 %)	NS
Frequency of postoperative fewer	5 (7.3 %)	3 (4.1 %)	NS
Duration of operation (min) (mean ± S.D.)	50.5 ± 19.2	41.6 ± 8.2	>0.05
Length of hospital stay (days) (mean ± S.D.)	5.0 ± 1.4	4.4 ± 0.7	>0.05

S.D. standard deviation, *NS* non significant

Most of the removed myomas were subserous or intramural: 48 subserous, 14 intramural and 6 pedunculated. Of these, 12 had multiple sites myomas (17.6 %), but we try to use always the same hysterotomy for neighbors fibroids.

Sites of myomas' removal were: fundal in 37 women (54.4 %), corporal in 22 (32.3 %) and around the lower uterine segment in 9 women (18.7 %), where we temporarily changed operation' steps just in 5 women. The average myoma' size was 8 cm (1.5–20), in 40 women, with 8 myomas measuring 4–6 cm, 14 myomas between 10 and 12 cm and >13 cm in 6 patients.

Differences in blood chemistry and surgical outcome in intracapsular cesarean myomectomy were not statistically significant ($p>0.05$) (Table 16.1)

Concerning the post-operative course, five patients had postpartum fever of 38.8 °C, on average, for 2 consecutive days after surgery (7.3 %); the blood culture didn't show any bacteria and patients were treated by large spectrum antibiotics. The average duration of hospitalization of intracapsular cesarean myomectomies was 5 days, with six patients requiring more than 5 days of hospital stay (8.8 %); these five patients felt too weak to be discharged, so they preferred to stay in the hospital an extra day.

There was no correlation between complications or duration of hospital stay and patient age, gravidity, parity or indication for CS.

None of the patients underwent repeated surgery after intracapsular cesarean myomectomy and no hysterectomy was required after intracapsular cesarean myomectomy.

Authors' data show no difference between intracapsular cesarean myomectomy group and control group, in term of pre and post-operative hemoglobin values, mean change in hemoglobin values, incidence of intraoperative hemorrhage, frequency of blood transfusion and of post-operative fever. The only two parameters that affect negatively the group submitted to intracapsular cesarean myomectomy are the duration of operation and the length of hospital stay.

Since obstetricians often confronted with fibroids while performing CS and face the dilemma of how they should be managed, considering the cost-benefit of our study, authors affirmed that intracapsular cesarean myomectomy procedure can be performed with some confidence, without affecting adversely the postoperative course and clinical outcomes.

Literature Drawbacks

Many studies on cesarean myomectomy presented in literature have significant drawbacks and possible biases: mostly of investigations on cesarean myomectomy are small sample size [15, 16, 30, 36, 64, 70, 71], data on type of anesthesia, laparotomy and gestational age during cesarean myomectomy are missing [18, 19, 54, 55, 72]; some authors reported the high use of oxytocin iv or intra-myometrium to reduce the hemorrhage

[33]; most of the studies does not provide any data about type of antibiotics and their dosage, although present the data about febrile morbidity and postoperative infections [15, 16, 63]; many reports reported myoma size diameter ranged from 2 to 200 mm, and some authors "operated" myomas 3×2×2 mm size [19]; significant number of studies does not mention average myoma size, type and localisation [16, 19]; incidence of perioperative transfusion ranged from 0 to 50 % [54, 70], and there are studies with emergency cesarean section and pregnants with low preoperative hemoglobin levels excluded [36].

Conclusion

In conclusion, performing additional surgical procedures on the uterus, as caesarean myomectomy, was relatively considered contraindicated for many years. Nevertheless, this dictum was not based on evidence, but rather on conjectural experience, which discouraged caesarean myomectomies with the exception of small pedunculated fibroids. The more recent medical literature, however, indicates that caesarean myomectomies are probably safe if performed for justified indications, by experienced surgeons and by using meticulous tissue handling techniques who avoid unnecessary hysterectomies as well as serious and life-threatening complications. There is a benefit in performing a single operation indicated anyhow rather than two. These situations are a challenge to the obstetrician and carry a legal dilemma because the patients need to be comprehensively informed, prior to surgery, as regarding size and location of the myoma during CS, and the possible complications to which a concomitant enucleation may lead. Even if any operation to be successful always needs adequate patient preparation, careful surgical planning by an experienced surgeon with the ability to correctly handle intra and postoperative complications.

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References

1. Novak ER, Woodruff JD. Myoma and other benign tumours of the uterus, Novaks' gynecologic and obstetric pathology with clinical and endocrine relations. Philadelphia: WB Saunders; 1979. p. 795–801.
2. Ouyang DW. Obstetric complications of fibroids. Obstet Gynecol Clin North Am. 2006;33:153–69.
3. Sparić R. Uterine myomas in pregnancy, childbirth and the puerperium. Srp Arh Celok Lek. 2014;142(1–2):118–24.
4. Rice JP, Kay HH, Mahony BS. The clinical significance of uterine leiomyomas in pregnancy. Am J Obstet Gynecol. 1989;160:1212–6.
5. Exacoustos C, Rosati P. Ultrasound diagnosis of uterine myomas and complications in pregnancy. Obstet Gynecol. 1993;82:97–101.
6. Katz VL, Dotters DJ, Droegemueller W. Complications of uterine leiomyomas in pregnancy. Obstet Gynecol. 1989;73:593–6.
7. Burton CA, Grimes DA, March CM. Surgical management of leiomyomata during pregnancy. Obstet Gynecol. 1989;74:707–9.
8. Hasan F, Arumugam K, Sivanesaratnam V. Uterine leiomyomata in pregnancy. Int J Gynaecol Obstet. 1991;34:45–8.
9. Vergani P, Locatelli A, Ghidini A, Andreani M, Sala F, Pezzullo JC. Large uterine leiomyomata and risk of cesarean delivery. Obstet Gynecol. 2007;109:410–4.
10. Coronado GD, Marshall LM, Schwartz SM. Complications in Pregnancy, Labor, and Delivery with Uterine Leiomyomas: a Population-Based Study. Obstet Gynecol. 2000;95:764–9.
11. Zizza A, Tinelli A, Malvasi A, Barbone E, Stark M, De Donno A, Guido M. Caesarean section in the world: a new ecological approach. J Prev Med Hyg. 2011;52(4):161–73.
12. Pei-Chun M, Yin-Chen J, I-De W, Chien-Han C, Wei-Min L, Cherng-Jye J. A huge leiomyoma subjected to a myomectomy during a cesarean section. Taiwan J Obstet Gynecol. 2010;49(2):220–2.
13. Sparić R, Lazović B. Inevitable cesarean myomectomy following delivery through posterior hysterotomy in a case of uterine torsion. Med Arh. 2013;67(1):75–6.
14. Shavell VI, Thakur M, Sawant A, Kruger ML, Jones TB, Singh M, Puscheck EE, Diamond MP. Adverse obstetric outcomes associated with sonographically identified large uterine fibroids. Fertil Steril. 2012;97(1):107–10.
15. Brown D, Fletcher HM, Myrie MO, Reid M. Caesarean myomectomy – a safe procedure. A retrospective case controlled study. J Obstet Gynaecol. 1999;19(2):139–41.
16. Ehigiegba AE, Ande AB, Ojobo SI. Myomectomy during cesarean section. Int J Gynecol Obstet. 2001;75:21–5.
17. Yellamareddygari S, Chakrabarti M, Ravuri S, Ahluwalia A. Leaving fibroids at cesarean section, is it safe? Gynecol Surg. 2010;7(2):173–5.

18. Kim YS, Choi SD, Bae DH. Risk factors for complications in patients undergoing myomectomy at the time of cesarean section. J Obstet Gynaecol Res. 2010;36(3):550–4.
19. Mu YL, Wang S, Hao J, Shi M, Yelian FD, Wang XT. Successful pregnancies with uterine leiomyomas and myomectomy at the time of caesarean section. Postgrad Med J. 2011;87(1031):601–4.
20. Edman CD, Toofanian A, MacDonald PC, Gant NF. Placental clearance rate of maternal plasma androstenedione through placental estradiol formation: an indirect method of assessing uteroplacental blood flow. Am J Obstet Gynecol. 1981;141: 1029–37.
21. Kauppila A, Koskinen M, Puolakka J, Tuimala R, Kuikka J. Decreased intervillous and unchanged myometrial blood flow in supine recumbency. Obstet Gynecol. 1980;55:203–5.
22. Palmer SK, Zamudio S, Coffin C, Stamm E, Parker S, Moore LG. Quantitative estimation of human uterine artery blood flow and pelvic blood flow redistribution in pregnancy. Obstet Gynecol. 1992;80: 1000–6.
23. Abnormalities of the reproductive tract. In: Cunningham FG, Leveno KL, Bloom SL, Hauth JC, Gilstrap LC III, Wenstrom KD, editors. Williams obstetrics, 22st ed. Mcgraw-Hill Medical Publishing Division. New York: NY, USA; 2005.
24. Ludmir J, Stubblefield PG. Surgical procedures in pregnancy. In: Gabbe SG, Niebyl JR, Simpson JL, editors. Gabbe: Obstetrics-Normal and problem pregnancies. 4th ed. New York: Churchill Livingstone, Inc; 2002. p. 613.
25. Haskins RD, Haskins CJ, Gilmore R, Borel MA, Mancuso P. Intramural leiomyoma during pregnancy becoming pedunculated postpartally. A case report. J Reprod Med. 2001;46:253–5.
26. Ben-Rafael Z, Perri T, Krissi H, Dekel A, Dicker D. Myomectomy during cesarean section-time to reconsider. In: Ben-Rafael Z, Diedrich K, Dudenhausen J-W, Mettler L, Schnider HPG, Shoham Z, editors. Controversies in obstetrics gynecology and infertility. Oren Publisher Ltd, International Proceedings Division, Israel; 2003, pp. 352–6.
27. Michalas SP, Oreopoulou FV, Papageorgiou JS. Myomectomy during pregnancy and caesarean section. Hum Reprod. 1995;10:1869–70.
28. Çelik C, Acar A, Çiçek N, Gezginc K, Akyürek C. Can myomectomy be performed during pregnancy? Gynecol Obstet Invest. 2002;53:79–83.
29. Hsieh TT, Cheng BJ, Liou JD, Chiu TH. Incidental myomectomy in cesarean section. Changgeng Yi Xue Za Zhi. 1989;12:13–20.
30. Dimitrov A, Nikolov A, Stamenov G. Myomectomy during cesarean section. Akush Ginekol (Sofia). 1999;38:7–9.
31. Omar SZ, Sivanesaratnam V, Damodaran P. Large lower segment myoma. Myomectomy at lower segment cesarean section A report of two cases Singapore. Med J. 1999;40:109–10.
32. Roman AS, Tabsh KM. Myomectomy at time of cesarean delivery: a retrospective cohort study. BMC Pregnancy Childbirth. 2004;4:14–7.
33. Kaymak O, Ustunyurt E, Okyay RE, Kalyoncu S, Mollamahmutoglu L. Myomectomy during cesarean section. Int J Gynecol Obstet. 2005;89:90–3.
34. Seffah JD. Re-laparotomy after cesarean section. Int J Gynecol Obstet. 2005;88(3):253–7.
35. Sparić R, Lazović B, Šulovic N, Buzadžić S. Our experience with intraoperative cell salvage during cesarean delivery in women with uterine myomas-four case reports and review of the literature. Med Pregl. 2014;67(3–4):111–7.
36. Kwawukume EY. Cesarean myomectomy. Afr J Reprod Health. 2002;6:38–43.
37. Sapmaz E, Celik H, Altungul A. Bilateral ascending uterine artery ligation vs tourniquet use for hemostasis in cesarean myomectomy A comparison. J Reprod Med. 2003;48:950–4.
38. Cobellis L, Florio P, Stradella L, Lucia ED, Messalli EM, Petraglia F, Cobellis G. Electro-cautery of myomas during caesarean section – two case reports. Eur J Obstet Gynecol Reprod Biol. 2002;102:98–9.
39. Desai BR, Patted SS, Pujar YV, Sherigar BY, Das SR, Ruge JC. A novel technique of selective uterine devascularization before myomectomy at the time of cesarean section: a pilot study. Fertil Steril. 2010; 94(1):362–4.
40. Wallach EE. Myomectomy. In: Thompson JD, Rock JA, editors. Te Linde's operative gynaecology. New York: JB Lippincott Company; 1992. p. 647–62.
41. Song D, Zhang W, Chames MC, Guo J. Myomectomy during cesarean delivery. Int J Gynaecol Obstet. 2013;121(3):208–13.
42. Frederick J, Fletcher H, Simeon D, et al. Intramyometrial vasopressin as a haemostatic agent during myomectomy. Br J Obstet Gynaecol. 1994;101(5):435–7.
43. Huijgen QC, Gijsen AF, Hink E, Van Kesteren PJ. Cervical tourniquet in case of uncontrollable haemorrhage during caesarean section owing to a placenta accreta. BMJ Case Rep. 2013;22:2013.
44. Ikeda T, Sameshima H, Kawaguchi H, Yamauchi N, Ikenoue T. Tourniquet technique prevents profuse blood loss in placenta accreta cesarean section. J Obstet Gynaecol Res. 2005;31(1):27–31.
45. DeLancey JO. A modified technique for hemostasis during myomectomy. Surg Gynecol Obstet. 1992; 174(2):153–4.
46. Fletcher H, Frederick J, Hardie M, Simeon D. A randomized comparison of vasopressin and tourniquet as hemostatic agents during myomectomy. Obstet Gynecol. 1996;87(6):1014–8.
47. Ginsburg ES, Benson CB, Garfield JM, et al. The effect of operative technique and uterine size on blood loss during myomectomy: a prospective randomized study. Fertil Steril. 1993;60(6):956–62.
48. Tulandi T, Murray C, Guralnick M. Adhesion formation and reproductive outcome after myomectomy and second- look laparoscopy. Obstet Gynecol. 1993;82(2):213–5.

49. Cobellis L, Messali EM, Stradella L, Pecori E, Gioino E, De Lucia E, et al. Myomectomy during cesarean section and outside pregnancy. Different outcomes of scars. Minerva Ginecol. 2002;54(6):483–6.
50. Cobbellis L, Messali EM, Satradella L, Pecori E, Cobellis G. Restitutio ad integrum of myometrium after myomectomy. Different results in pregnant and nonpregnant patients. Minerva Ginecol. 2002;54(5): 393–5.
51. Lee HJ, Cho DH. Myomectomy using purse-string suture during cesarean section. Arch Gynecol Obstet. 2001;283 Suppl 1:835–7.
52. Adesiyn AG, Ojabo A, Durosinlorun-Mohammed A. Fertility and obstetric outcome after cesarean myomectomy. J Obstet Gynecol. 2008;28(7):710–2.
53. Pallasmaa N, Ekblad U, Aitokallio-Tallberg A, Uotila J, Rudaskoski T, Ulander VM, et al. Cesarean delivery in Finland: maternal complications and obstetric risk factors. Acta Obstet Gynecol Scand. 2010;89(7):896–902.
54. Hassiakos D, Christopoulos P, Vitoratos N, Xarchoulakou E, Vaggos G, Papadias K. Myomectomy during cesarean section: a safe procedure? Ann N Y Acad Sci. 2006;1092:408–13.
55. Agrawal K, Agrawal L, Agrawal A, Agrawal VK, Agrawal K. Caesarean myomectomy: prospective study. NJIRM. 2011;2(3):11–4.
56. Mahendru R, Sekhon PK, Gaba G, Yadav S. At times, myomectomy is mandatory to effect delivery. Ann Surg Innov Res. 2011;5(1):9.
57. Aksoy AN, Saracoglu KT, Aksoy M, Saracoglu A. Unavoidable myomectomy during cesarean section: a case report. Health. 2011;3(3):156–8.
58. Liu WM, Wang PH, Tang WL, Wang IT, Tzeng CR. Uterine artery ligation for treatment of pregnant women with uterine leiomyomas who are undergoing cesarean section. Fertil Steril. 2006;86(2):423–8.
59. Sparić R, Berisavac M, Buzadžić S, Mirković LJ. Complications during cesarean delivery in a patient with two previous myomectomies. Acta Chir Iugosl. 2013;60(1):99–100.
60. Rich DA, Stokes IM. Uterine torsion due to a fibroid, emergency myomectomy and transverse upper segment caesarean section. BJOG. 2002;109(1):105–6.
61. Owolabi AT, Oluwafemi K, Loto OM, Makinde ON, Adeyemi AB. Caesarean myomectomy – a safe procedure: a retrospective case controlled study. N J Obstet Gynaecol. 2007;2(2):59–62.
62. Yuddandi N, Gleeson R, Gillan J, Geary M. Management of massive caseous fibroid at caesarean section. J Obstet Gynecol. 2004;24(4):455–61.
63. Simsek Y, Celen S, Danisman N, Mollamahmutoglu L. Removal of uterine fibroids during cesarean section: a difficult therapeutic decision. Clin Exp Obstet Gynecol. 2012;39(1):76–8.
64. Adesiyn AG, Ameh AC, Ojabo A. Myomectomy at caesarean section; descriptive study of clinical outcome in a tropical setting. J Ayub Med Coll Abbottabad. 2009;21(4):7–9.
65. Tinelli A, Malvasi A, Hurst BS, Tsin DA, Davila F, Dominguez G, et al. Surgical management of neurovascular bundle in uterine fibroid pseudocapsule. JSLS. 2012;16:119–29.
66. Malvasi A, Cavallotti C, Morroni M, Lorenzi T, Dell'Edera D, Nicolardi G, et al. Uterine fibroid pseudocapsule studied by transmission electron microscopy. Eur J Obstet Gynecol Reprod Biol. 2012;162:187–91.
67. Tinelli A, Hurst BS, Hudelist G, Tsin DA, Stark M, Mettler L, et al. Laparoscopic myomectomy focusing on the myoma pseudocapsule: technical and outcome reports. Hum Reprod. 2012;27:427–35.
68. Tinelli A, Malvasi A, Hudelist G, Cavallotti C, Tsin DA, Schollmeyer T, Bojahr B, Mettler L. Laparoscopic intracapsular myomectomy: comparison of single versus multiple fibroids removal. An institutional experience. J Laparoendosc Adv Surg Tech A. 2010;20(8):705–11.
69. Tinelli A, Malvasi A, Mynbaev OA, Barbera A, Perrone E, Guido M, Kosmas I, Stark M. The surgical outcome of intracapsular cesarean myomectomy. A match control study. J Matern Fetal Neonatal Med. 2014;27(1):66–71.
70. Machado LS, Gowri V, Al-Riyami N, Al-Kharusi L. Caesarean myomectomy: feasibility and safety. Sultan Qaboos Univ Med J. 2012;12(2):190–6.
71. Sudhir A, Sebanti G. Cesarean myomectomy – a study of 14 cases. J Obstet Gynecol India. 2006;56(6):486–8.
72. Li H, Du J, Jin L, Shi Z, Liu M. Myomectomy during caesarean section. Acta Obstet Gynecol Scand. 2009;88(2):183–6.

Complications of Myomectomy

17

Richard J. Gimpelson and David Jay Levine

Introduction

The potential complications associated with myomectomy can be encountered regardless of the surgical approach. This chapter addresses the complications specific to the laparoscopic and trans-cervical or hysteroscopic approaches. Each potential complication will be discussed with the intent to prevent its occurrence. However should these complications occur the subsequent discussion should help the surgeon manage and or correct the complication

Complications of Hysteroscopic Myomectomy

Any complication that can occur during hysteroscopic surgery can occur during hysteroscopic myomectomy. Some of these complications are more common with myomectomy such as bleeding, excess fluid absorption, cervical injury, uterine perforation, and intra-abdominal organ injury. These complications can be prevented nearly all the time by careful attention to technique and knowing when to stop.

The author has promoted the following advice to all who perform hysteroscopy: "*One who scopes and walks away can always scope another day*".

This advice is extremely appropriate for avoiding complications of hysteroscopic myomectomy.

Preoperative Preparation

Prior to hysteroscopic myomectomy, a number of measures will reduce intraoperative surprises and thus reduce complications:

- Hemoglobin: Since many of these women are experiencing abnormal uterine bleeding that can be heavy and prolonged, hemoglobin measured at the time of the first visit will reduce the chance of bringing the patient to surgery with severe anemia.
- Pelvic/transvaginal ultrasound (Fig. 17.1a) and saline infusion sonogram will reveal adnexal abnormalities, multiple leiomyomata, intracavitary leiomyomata, and transmural leiomyomata (Fig. 17.1b). The knowledge of an adnexal mass or transmural leiomyoma will make laparoscopy integral to the success of the procedure.

Opinion of author is of Dr. Gimpelson RJ, based on 32 years performing operative hysteroscopy

R.J. Gimpelson
Minimally Invasive Gynecology,
Department of Obstetrics and Gynecology,
Mercy Hospital St Louis, St Louis, MO, USA
e-mail: rgimpelson@aol.com

D.J. Levine, MD (✉)
Minimally Invasive Gynecologic Surgery,
Department of Obstetrics and Gynecology,
Mercy Hospital St Louis, St Louis, MO, USA
e-mail: levine-d@sbcglobal.net

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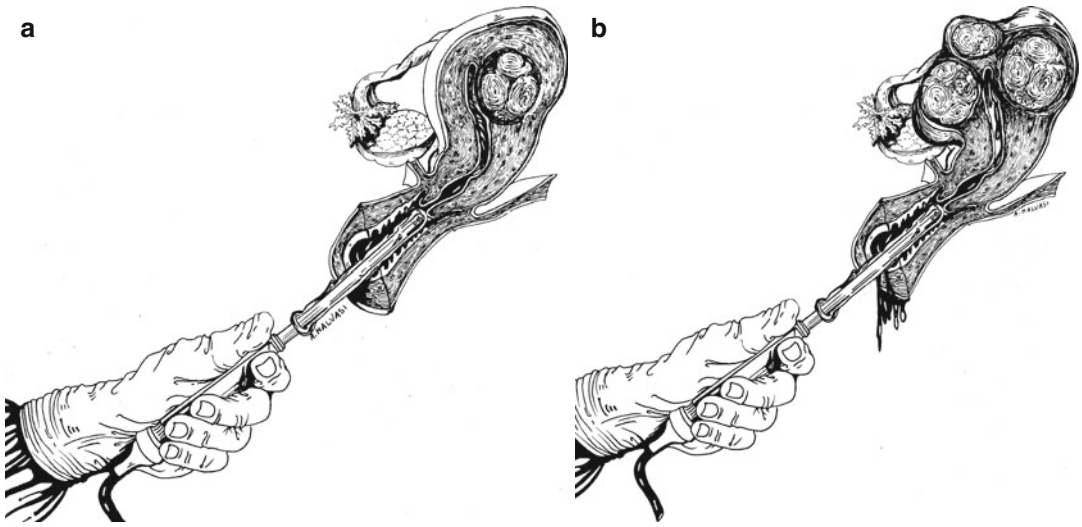

Fig. 17.1 (**a**) Transvaginal longitudinal ultrasonographic uterine scan with submucous myoma located in posterior uterine wall. (**b**) Preoperative transvaginal ultrasonographic scan showing fundal and corporal myomas

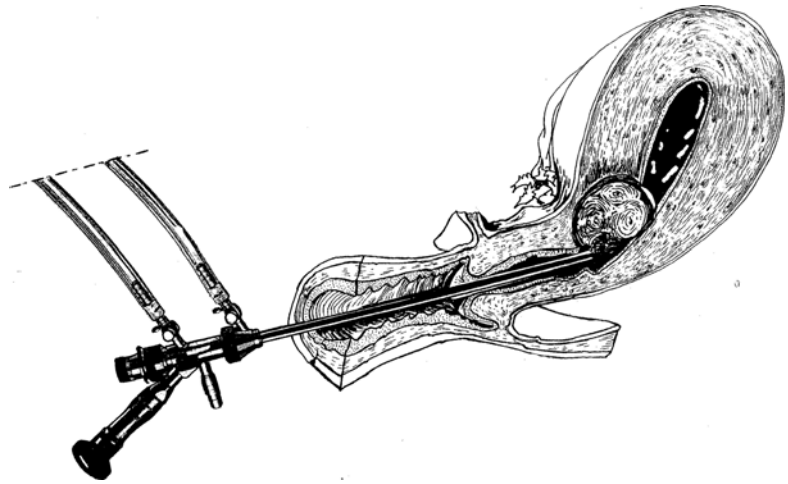

Fig. 17.2 A difficult operative hysteroscopy to remove a cervical-isthmic myoma for a stenotic uterine cervix

The common advice is to perform hysteroscopic myomectomy during the early proliferative phase of a cycle; however, some of these patients bleed nearly every day and some are anovulatory, so timing can be a problem. In addition, work, school, and personal activities are also factors in scheduling surgery. It is critical that one must be able to do hysteroscopic myomectomy anytime during the menstrual cycle because nature does not always cooperate.

The preoperative exam will make the gynecologist aware of cervical stenosis (Fig. 17.2) which can make uterine entry difficult, resulting in cervical lacerations or uterine perforation.

A 2–4 mm diameter Laminaria japonica can be inserted into the cervical canal on the day prior to surgery. This will usually dilate the cervix enough to allow intraoperative dilation and insertion of hysteroscopic instrumentation. The easier method is the administration of 400 μg of oral Misoprostol 12–24 h prior to surgery [1].

Vaginal administration of 400 μg of Misoprostol has also been shown to adequately soften and dilate the cervix [2].

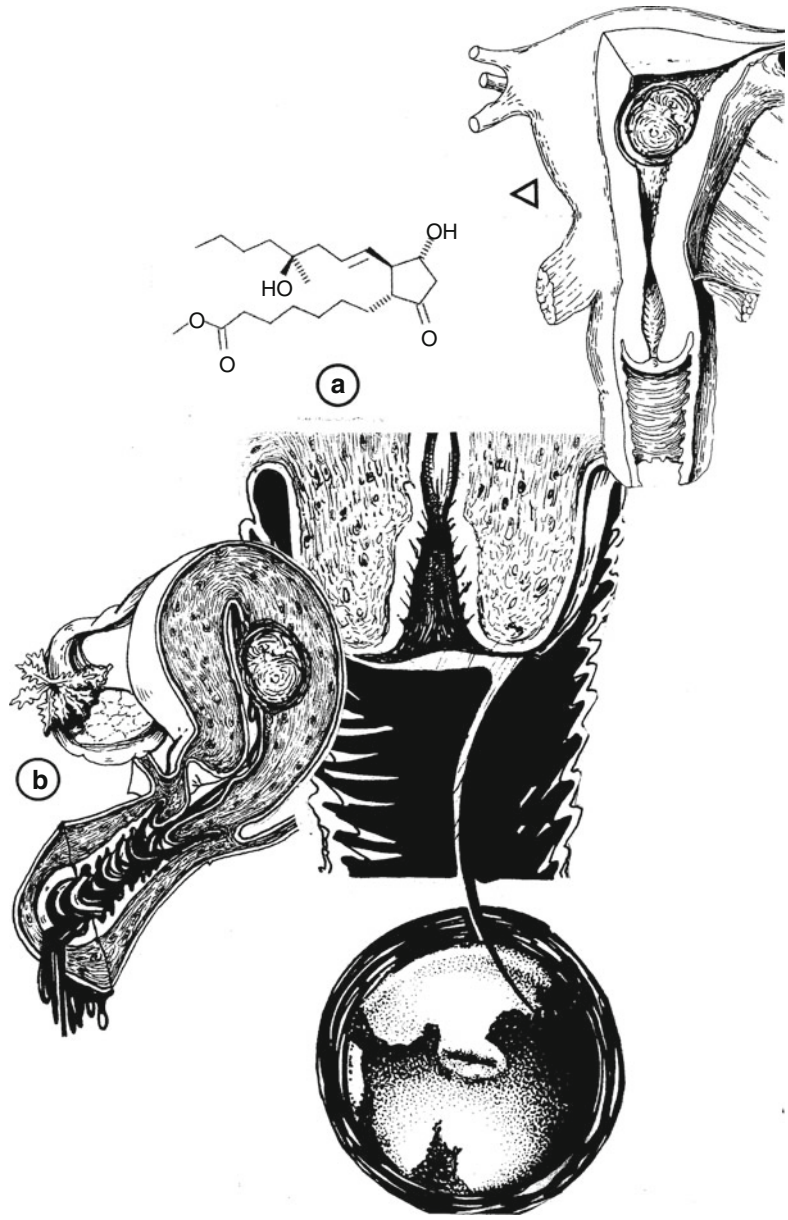

Fig. 17.3 Preoperative examination of stenotic uterine cervix (**b**) prior to hysteroscopic myomectomy, where it is suggested the use of misoprostol at 200 mcg (**a**) to stimulate cervical dilatation

The author has had the patient insert 200 mcg of Misoprostol intravaginal 8–10 h prior to surgery with excellent results (Fig. 17.3).

Cervical Laceration

If a cervical laceration occurs in spite of the above techniques, it will either be from the tenaculum on the external cervix or from cervical dilation resulting in laceration of the endocervical canal or cervical-uterine junction. Both types of lacerations are the result of excess force while inserting the hysteroscope.

Besides the Laminaria or Misoprostol, 4 units of Vasopressin injected into the cervix has been shown to significantly reduce the force required to dilate the cervix [3].

The author has utilized 2 units of Pitressin in 10 cc saline with similar results and has noted a

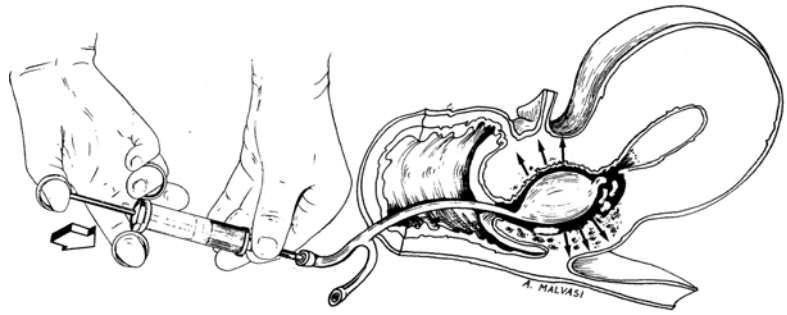

Fig. 17.4 A Foley catheter using after cervical laceration during hysteroscopic myomectomy to stop bleeding

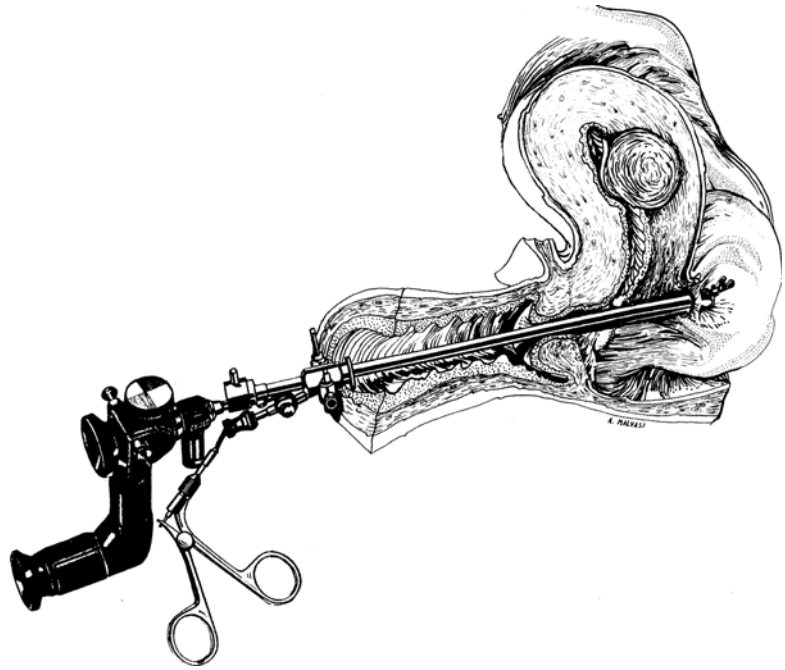

Fig. 17.5 Uterine perforation of posterior wall and bowel loop, adherent to uterus, during hysteroscopic myomectomy

decrease in bleeding from the tenaculum and injection sites.

The external cervical lacerations are easily treated with interrupted or figure of eight absorbable suture. Lacerations of the endocervical canal are more concerning than external lacerations. Heavy bleeding and excess fluid can occur with lacerations of the cervical canal.

If the laceration is at the cervical-uterine junction, one can insert a Foley catheter into the uterine cavity (Fig. 17.4). The balloon is filled with 10–15 cc saline and pulled against the junction to act as a tamponade and also a drain to monitor the bleeding. If bleeding continues, one must suture the cervical branches of the uterine artery and if bleeding still does not stop, a hysterectomy may be the only option [4].

Uterine Perforation

Uterine perforation occurs in approximately 1–2 % of all hysteroscopic procedures [5, 6] and 2–3 % in hysteroscopic myomectomies [7, 8].

Perforation with sound, dilator, hysteroscope (Fig. 17.5), without instrumentation or energy, usually just requires cessation of the procedure and observation.

Serious complications are unlikely and complete blood count in 24 h is usually all that is needed. An ultrasound may also be performed. If there are signs of peritonitis, bowel injury must be ruled out by laparoscopy or laparotomy [4].

If perforation occurs with scissors, forceps, or active electrode, the risk to intra-abdominal

structures is much more likely and laparoscopy or laparotomy should be seriously considered [9].

The author advises initial uterine entry under direct visualization with a hysteroscope to dilate the cervix and evaluate the uterine cavity.

Once the hysteroscope has been inserted and removed, the resectoscope or morcellator can often be inserted without the need for use of dilators. It should be noted that the preoperative ultrasound and saline infusion sonogram will document fibroid depth, and thus one can avoid resecting a transmural myoma. Simultaneous ultrasound monitoring may be helpful whenever a hysteroscopic myomectomy is anticipated in which a significant intramural component is present [10].

The author has utilized the preoperative ultrasound to measure the distance from the leiomyoma to serosa (Fig. 17.6).

If there is at least 3 mm of myometrium, a partial myomectomy is performed.

The patient is then brought back for a repeat procedure and the leiomyoma has usually migrated significantly into the uterine cavity and can be easily resected in its entirety.

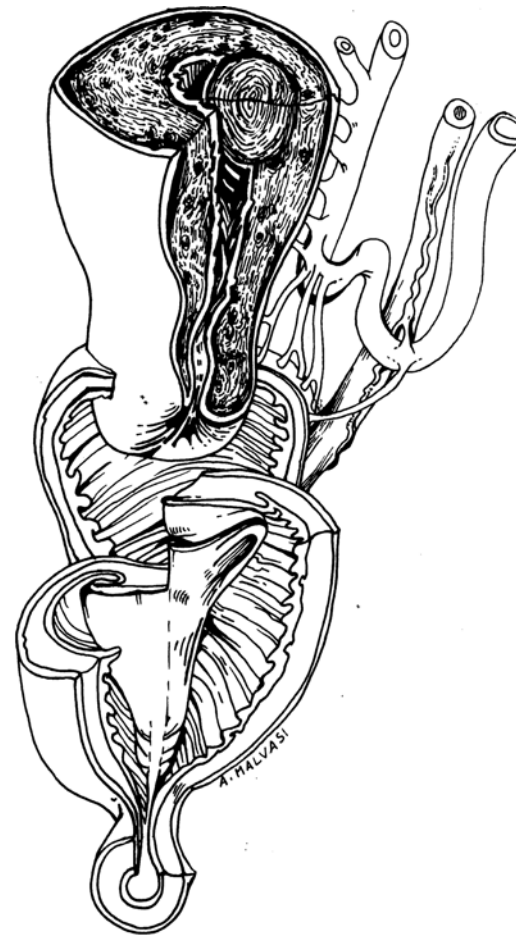

Fig. 17.6 The measurement of distance between subserosal myoma and uterine serosa before hysteroscopic myomectomy

Fluid Intravasation

Fluid intravasation is a most serious but easily avoided complication if one pays meticulous attention to inflow and outflow volumes. There are several fluid pumps available. It is important that the gynecologist be familiar with that pump and also have the assistant in the room report the deficit at frequent intervals. If mechanical or bipolar resectoscope is being used, the distention media of choice is normal saline.

One should work at the lowest flow and pressure that still provides good visualization. In general, a deficit of 2,000 ml of saline is considered the maximal amount allowed. Once intravasation of saline goes over 2,000 ml, 20 mg of intravenous furosemide should be given, serum electrolytes drawn, and the procedure ended [11].

The margin of safety for fluid intravasation of nonconductive media used with the monopolar resectoscope is much less than that allowed with saline. The reason is that in healthy women, saline overload is easily managed with a diuretic; however, nonconductive fluid overload results in hyponatremia which has much more serious consequences.

Depending on the level of hyponatremia, manifestations include headache, restlessness, vomiting, confusion, cyanosis, arrhythmia, seizures, cerebral edema, brain herniation, and death. Thus, immediate treatment is necessary.

The overall incidence of excess fluid intravasation ranges from 1 to 4 % [12, 13].

Limits for non-conductive media intravasation are generally 750–1,200 ml.

Obviously, women with medical problems should have lower limits for both conductive and non-conductive media.

An equation developed by Wortman has been used to calculate maximum allowable fluid absorption limit (MAFA limit) for nonconductive media.

In addition, he has developed excellent guidelines for management of hyponatremia [4].

$$\text{MAFA limit} = 17.6\text{ml/kg} \times \text{body weight}(\text{kg}).$$

This equation is for a healthy woman without cardiac, liver, or renal disease. Under no circumstances should a MAFA limit be more than 2 L since few data points are available for women weighing over 125 kg.

With serum sodium concentrations between 130 and 140 mEq/L, no treatment is needed.

With serum sodium concentrations absent signs or symptoms of encephalopathy, fluid restriction and furosemide can be utilized for management.

An intensivist should be consulted for any serum sodium concentration below 120 mEq/L or if any evidence of encephalopathy regardless of serum sodium concentration.

Bleeding

Bleeding following hysteroscopic myomectomy ranges from 1 to 21 % [8, 14].

Most bleeding stops shortly after the procedure is ended.

If bleeding persists, tamponade can be achieved by inserting a Foley catheter with 10–15 cc saline in the balloon and the tip of the catheter cut off. This procedure works nearly all the time.

In addition, 0.2 mg Methergine can also be given IM.

If this fails, one must consider uterine artery embolization, uterine artery ligation or hysterectomy.

Before one resorts to the three above measures, a second examination of the uterine cavity should be performed in the event that a single bleeding site can be coagulated. One must be very cautious when resecting leiomyomata in the lateral lower uterine segment, as this is where the larger vessels enter the uterus.

This is why mapping the location of the leiomyomata by ultrasound and saline infusion sonogram prior to surgery is important.

Gas Embolism

Although usually asymptomatic, gas embolism occurs frequently with use of the resectoscope in hysteroscopic surgery. The gas embolism should be differentiated from air embolism which is more likely to be serious and even fatal. Air embolism probably occurs from not purging room air out of the inflow line and is easily avoided by making sure the distention fluid has run completely through the inflow line before inserting the scope into the cervical canal.

Gas embolism, on the other hand, occurs from the effect of monopolar or bipolar electrical energy on tissue and distention media. The major components of electro-surgical gases generated by both bipolar and monopolar electrosurgery are hydrogen, carbon monoxide, and carbon dioxide [15].

The amounts of generated gases are relatively equal in both bipolar and monopolar electrosurgery with increasing amounts related to increasing power.

An early sign of gas embolism is a drop in end–tidal CO_2 or drop in oxygen saturation (Fig. 17.7).

Management involves early recognition and interruption of gas to open venous channels.

This involves immediately removing the resectoscope.

The problem is usually self limiting and once the patient stabilizes, the procedure is ended.

The easiest way to reduce the risk of gas embolism is to operate at the lowest intrauterine pressure possible and at the lowest effective power [16].

Infection

Infection is relatively uncommon with hysteroscopic myomectomy with a rate of 0.4 % reported in a collection of over 1,000 cases [17] (Fig. 17.8).

The author recommends prophylactic antibiotics for hysteroscopic myomectomy.

Adhesions

Adhesion formations following myomectomy in infertility patients are managed by a second look procedure 4–5 weeks after completion of myomectomy.

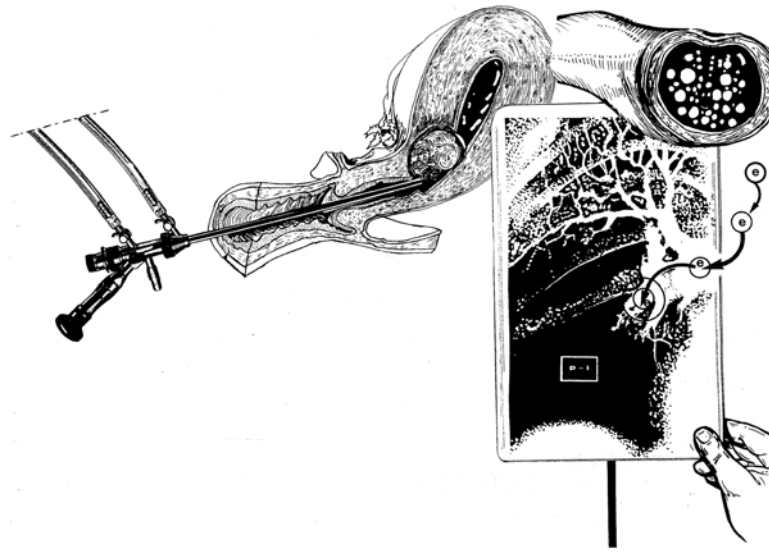

Fig. 17.7 Pulmunar embolism during hysteroscopic myomectomy (*e* embolism, *P.I.* pulmonary ischemia)

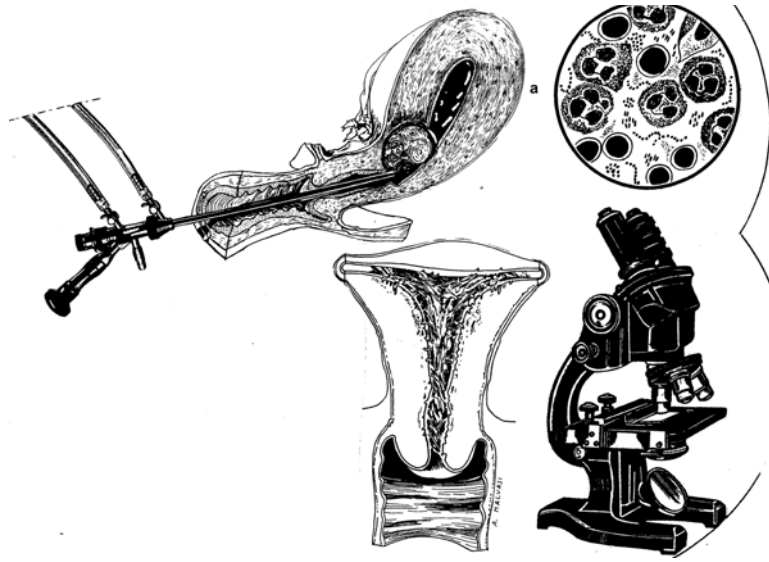

Fig. 17.8 Infections during hysteroscopic myomectomy (*a*); Asherman syndrome after hysteroscopic myomectomy

Complications of Laparoscopic Myomectomy

Laparoscopic myomectomy (Fig. 17.9) offers the same advantages over laparotomic myomectomy, namely quicker recovery decreased blood loss and less pain in the immediate post operative period. These benefits are weighed against the suggestion that closure of the myometrial defect and control of intraoperative bleeding is more difficult using a laparoscopic approach. Multiple retrospective studies have evaluated the outcomes and complications of myomectomy either performed laparoscopically or via laparotomy and they are the same [18].

Some of these complications are inherent to the procedure and may occur regardless of operative approach. The most described major complications are intraoperative hemorrhage, uterine hematomas, uterine rupture, undiagnosed sarcomas, bowel or ureteral damage, adenomyosis and leiomyomatosis.

The more commonly experienced minor complications are urinary tract infections and

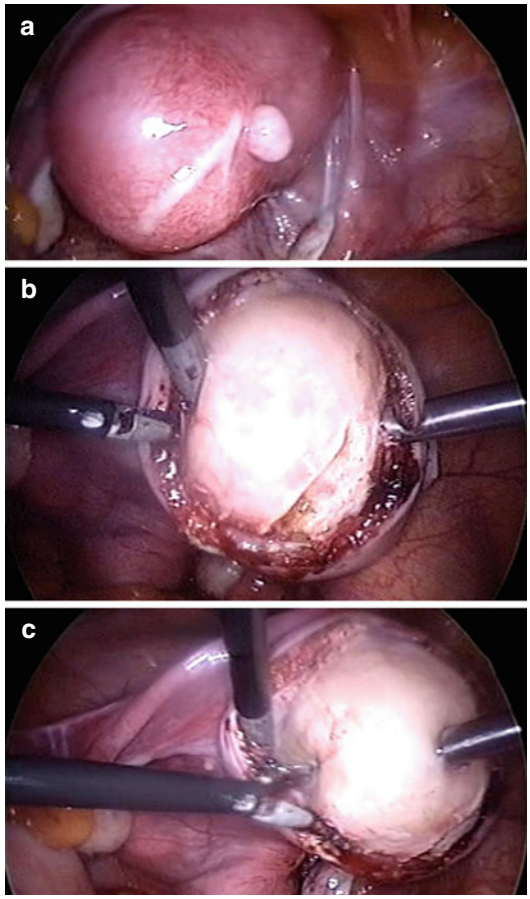

Fig. 17.9 A laparoscopic myomectomy: (**a**) incision of uterine serosa; (**b**) delicate dissection of myoma from its myoma pseudocapsule; (**c**) enucleation of myoma

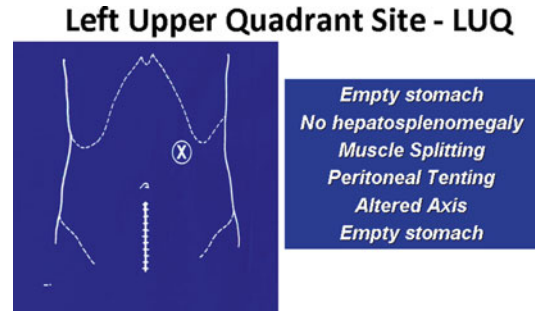

Fig. 17.10 Insufflation and visualization of the abdomen can be safely accomplished with the use of a left upper quadrant port placed at Palmer's point

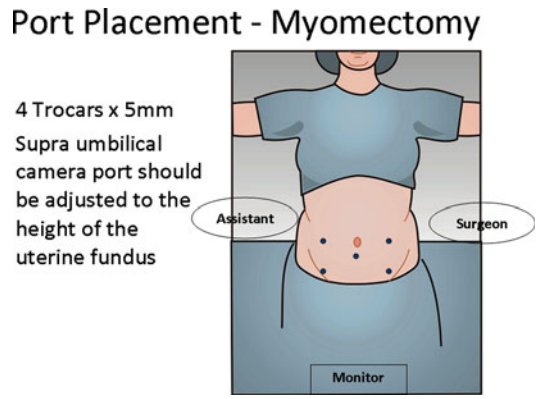

Fig. 17.11 The surgeons and laparoscopic ports should be placed in relation to the myomatous uterus

transient postoperative fever. All of these complications will be discussed in this chapter as well as suggestions to prevent them from occurring.

Laparoscopic Myomectomy

Inherent in any laparoscopic procedures are the potential risks associated with laparoscopy itself. The risks and complications are related to abdominal entry and placement of operating ports. The addition of a large uterus irregularly shaped by multiple fibroids will distort and compromise the capacity of the abdominal cavity.

Insufflation and visualization of the abdomen can be safely accomplished with the use of a left upper quadrant port placed at Palmer's point (Fig. 17.10).

This vantage point not only prevents damage to the great vessels and bowel during initial entry but allows the surgeon to visually gauge where the operating and laparoscopic ports should be placed in relation to the myomatous uterus (Fig. 17.11).

Visualizing the anatomical path of the inferior epigastic vessels before lateral port placement and introducing the lateral ports, perpendicular to the abdominal wall prevent vessel laceration (Fig. 17.12).

Once the individual fibroids have been identified, the serosal layer overlying the fibroid is injected with a solution of dilute vasopressin to minimize blood loss. A cutting device is used to incise the serosa to reach the

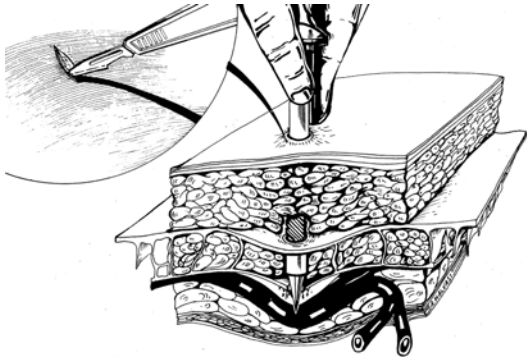

Fig. 17.12 Perpendicular introduction of accessory port avoiding the inferior epigastric vessels

fibroid capsule and once reached sharp and blunt dissection is used to free the myoma from its bed. During the myomectomy care must be exercised to always be aware of the position of the sharp (single tooth tenaculum) and electrical instruments to prevent inadvertent damage. Interligamentous fibroids which are in close proximity to the uterine vessels and ureters can pose a strategic dilemma. They are usually peduculated or subserosal and can be approached by transecting the peritoneum posteriorly and dissecting the areolar tissue away from the side wall [19].

Laparoscopic or robotic myomectomy could be very dangerous, especially in case of myoma located into broad ligament, for the possible uterine artery injuries (Fig. 17.13) or ureteral lesions (Fig. 17.14), consequently to anatomic dislocation of such structures for myoma positioning. Once the myomas have been removed from the uterine musculature and the myometrial defect or defects have been repaired, the myomas can be removed from the abdomen utilizing a variety of different methods. Morcelation has been the method of choice for the removal of fibroids over the past 20 years. Hand morcelators were replaced by power devices to expedite the process and ease the physical burden on the surgeon. Morcelation could also be performed through minilaparotomy or colpotomy if intrabdominal morselation was not an option. The advantages and disadvantages will be discussed more thoroughly later the chapter.

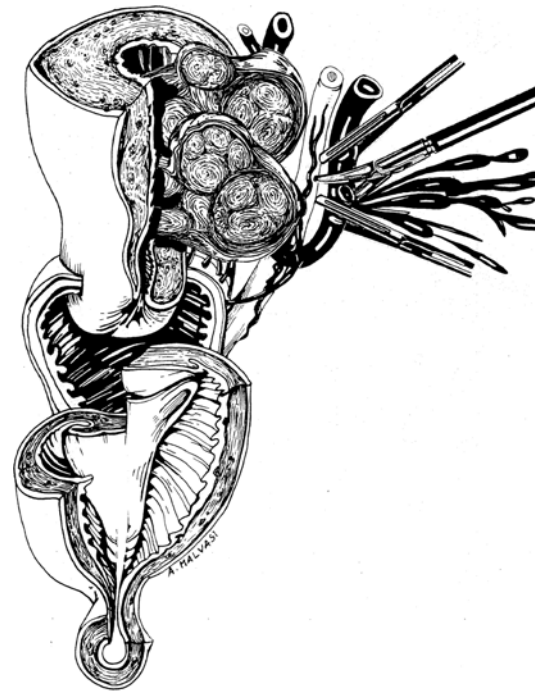

Fig. 17.13 Accidental surgical resection of left uterine artery with laparoscopic Mayo scissors, during myomectomy of infraligamentary left myoma

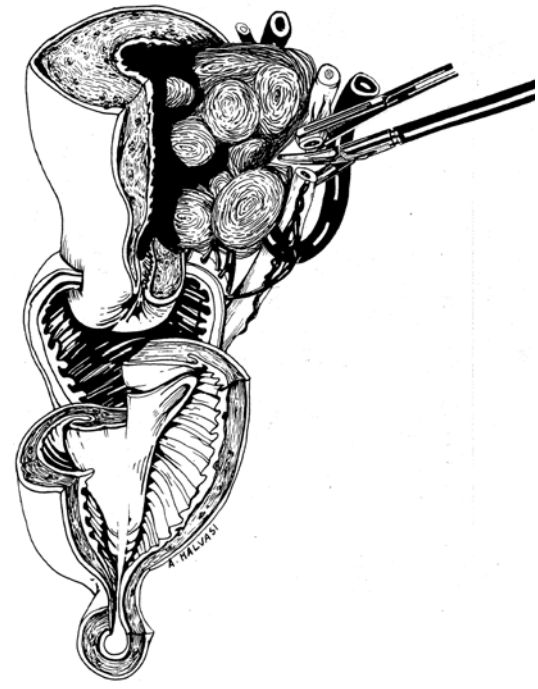

Fig. 17.14 Complete ureteral section with Mayo scissors during laparoscopic myomectomy, with enucleation of a large myoma located into left broad ligament

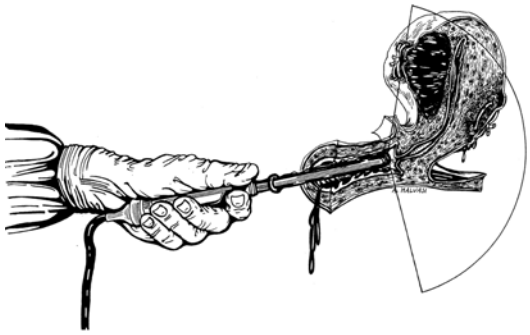

Fig. 17.15 Post laparoscopic myomectomy myometrial hematoma, located into anterior uterine body

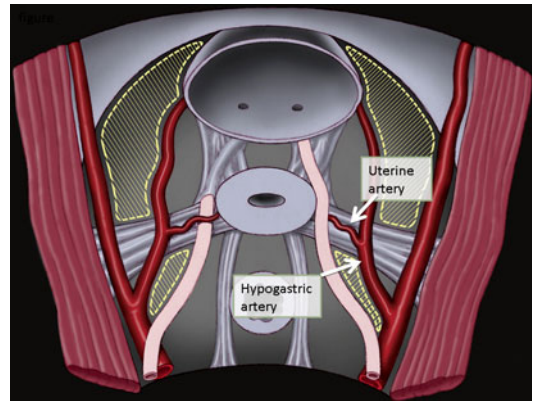

Fig. 17.16 The retroperitoneal space image: identification of the ureters and uterine arteries (to clip or coagulate in case of hemorrhage)

Management of Intraoperative Bleeding

Intraoperative bleeding is traditionally a major concern when performing a myomectomy. When performed via laparotomy the uterine as well as the utero-ovarian blood supply can be interrupted using techniques to physically occlude the vasculature. Laparoscopically however these techniques are not available and vasoconstriction is accomplished using a preparation of dilute Pitressin (20 U in 1–200 cc of normal saline) injected into the plane between the myoma and the surrounding myometrium. The vasoconstrictive as well as a myometrial contractive effect will last for 30 min. Care must be taken not to inject the Pitressin intravascularly which can result in bradycardia, hypotention, pulmonary edema and cardiac arrest. After the tissues are adequately blanched confirming the vasoconstrictive effect, an incision is made down to the myoma capsule. Once inside the myoma/myometrial plane the dissection is bloodless until the base of the myoma is reached which is often more vascular. Minimal use of electocautery to control bleeding is advised so as not to devascularize the myoma bed. Such overuse of electrical hemostasis has been shown to weaken the subsequent uterine repair.

Uterine hematomas (Fig. 17.15) are the result of inadequate myometrial reapproximation and hemostasis. This may interfere with growth factors and the production of excess collagen deposition leading to poor wound healing during the incisional closure process. As will be discussed more thoroughly later the multilayer closure of the myometrial defect is necessary to prevent subsequent uterine rupture [20].

In case of severe hemorrhage bilateral uterine artery or hypogastric ligation can be performed by opening the retroperitoneal space identifying the ureters and clipping or coagulating the vessels (Fig. 17.16).

This will control the active bleeding so that the uterine defects can be closed.

Uterine Rupture

Uterine rupture can be a devastating event during pregnancy threatening the life of both mother and baby (Figs. 17.17 and 17.18). The incidence of uterine rupture after previous myomectomy is less than 1 % when performed either via laparoscopy or laparotomy [18].

Factors that contribute to weakness in uterine wall integrity include overzealous use of electrocautery and the inadequate caliber of suture utilized for hemostasis. Retrospective analysis of uterine ruptures indicate the use of 3/O and 4/O suture instead of the traditional O suture which contributes to intramural hematomas, indentations and fistulas [19].

When examining the traditional technique employed for closure of the myometrial defect during laparotomic myomectomy one finds some

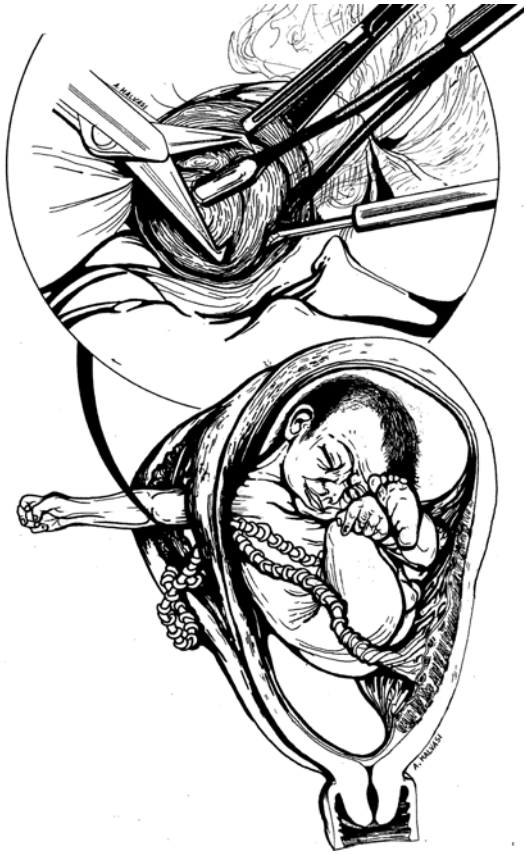

Fig. 17.17 Uterine rupture during late pregnancy in patient after laparoscopic myomectomy with excessive elettrocoagulation on myometrium during myoma enucleating

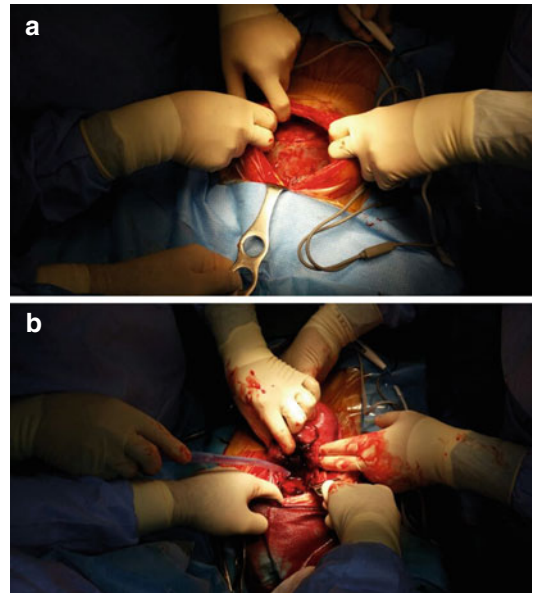

Fig. 17.18 A uterine rupture at 21 weeks of pregnancy: (**a**) urgent longitudinal laparotomy with abdomen opening: it is possible to see the abdominal cavity below the placenta which floats between the bowel loops, after being expelled from the uterine wall torn at the site of a previous myomectomy; (**b**) uterine exposure to the outside of the abdomen with evidence of a large laceration on the anterior wall at the site of rupture, where previously had been removed an intramural myoma

basic rules. The myoma is traditionally extracted using a scalpel and hemostasis is controlled mechanically rather than the use of electrocautery. The defect is than closed in multiple layers using interrupted mattress sutures of O caliber suture. When examining the 19 uterine ruptures described by Parker et al., the majority were either not closed at all or were sutured in one layer only [21].

A similar review reported seven uterine ruptures after myomectomy over a 3 year period where the excessive use of electocautery to manage hemostasis was described. In only two cases was a double layer closure utilized. This deviation from the traditional management of the myoma bed as would be performed via laparotomy can lead to a decrease in the integrity of the uterine wall and increase the risk of uterine rupture [22].

Recently the use of uni or bidirectional barbed suture has made the closure of the myometrial defect less labor intensive. When comparing barbed versus traditional suture closure of a hysterotomy in the animal model there was no difference in adhesion formation [23].

In a recent review of hysterecomy and myomectomy data utilizing barbed suture the only reported complication with its use was a small bowel obstruction caused by leaving a long tail at the end of the suture line. As a result it has been suggested that the suture be cut close to the tissue to prevent complication [24].

Further Complications After Myomectomy

Other possible complications after laparoscopic myomectomy include bladder lesions, particularly during dissections of bladder wall from

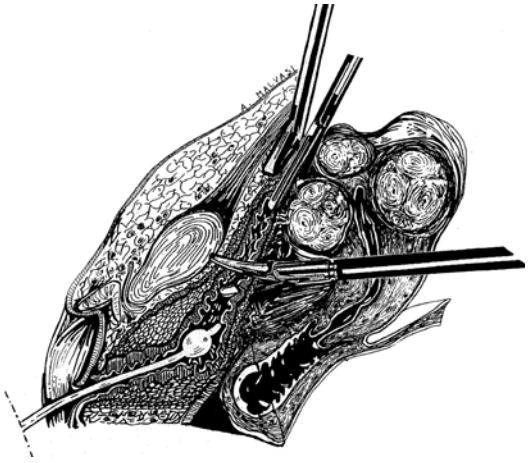

Fig. 17.19 Erroneous bladder incision with laparoscopic scissors during adhesions' removal between posterior bladder wall and anterior uterine body, in a patient with two previous cesarean section

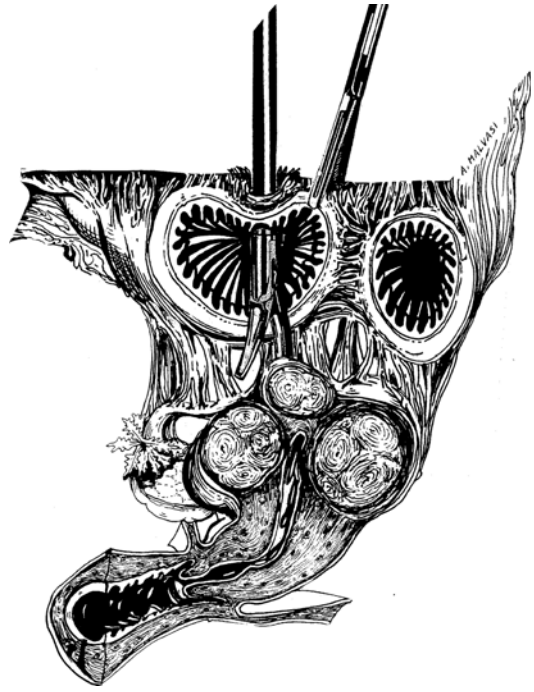

Fig. 17.20 Bowel perforation during laparoscopic adhesions removal for a successive myomectomy

uterine wall, for the adhesions removal (Fig. 17.19). laparoscopic bowel injuries are also possible during adhesion removal in patients with previous appendectomy or peritonitis. Bowel is often found densely adherent to fibroids or to the defects created after previous myomectomy (Figs. 17.20, 17.21, and 17.22).

Sarcoma

A very unusual but potentially life altering complication is that of an undiagnosed uterine sarcoma. The most common being leiomyosarcoma however endometrial stromal and carcinosarcoma have also been described. They have an incidence of between .13 and .29 % [18] more commonly found between the fourth and seventh decade. It can be suspected in a single myoma which is found enlarging in a postmenopausal woman (Fig. 17.23). Unfortunately there are no clear diagnostic criteria to predict a leimyosarcoma.

MRI has been used to try to distinguish between benign myomata demonstrating degenerative and hemorrhagic qualities and the more diffuse degenerative changes associated with a leiomyosarcoma. Irregular central zones of low attenuation found in uterine sarcomas are not specific for sarcoma but when identified may alter ones surgical approach if malignancy is suspected [25].

Some have suggested an endometrial biopsy in all cases to be morselated which may identify an occult endometrial malignancy. The addition of serum LDH increases the positive predictive value and sensitivity when included in the preoperative evaluation of suspected myomata [26].

The obvious concern is the peritoneal spread via morselation of an undiagnosed malignant tumor which will upgrade the staging and potentially change the already poor prognosis. Considering the significance of sarcomatous spread during morcellation, the use of an endobag or morcellation via cold knife through a mimi laparotomy or colpotomy is being suggested. Regardless of the route of tissue removal a more in depth consent must be given to include he possibility of an undiagnosed sarcoma. The surgeon and the patient must agree on the amount of risk they are willing to accept based on all available information. If a morcellated specimen is identified with sarcoma early reoperation and proper staging is necessary.

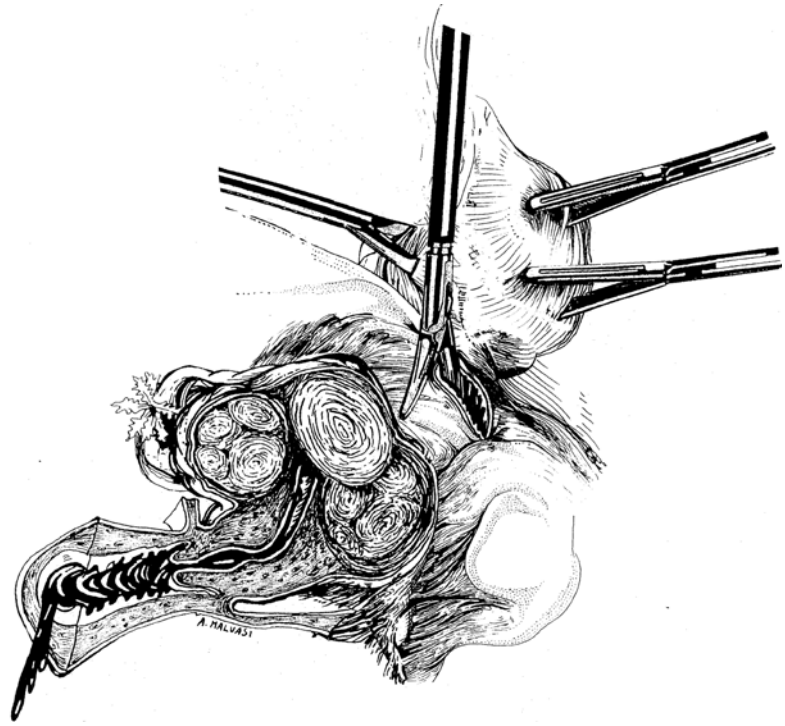

Fig. 17.21 Intestinal injury of bowel loop strictly adherent to uterine fundus, by laparoscopic scissor during myomectomy

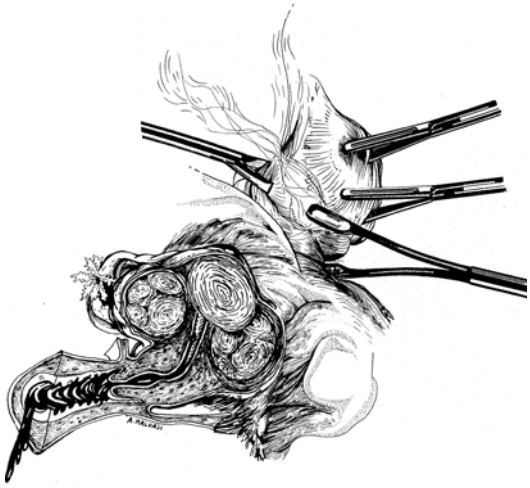

Fig. 17.22 Bowel wall lesions during laparoscopic myomectomy, by bipolar forceps during a severe and diffuse adhesions removal from uterine serosa over myoma

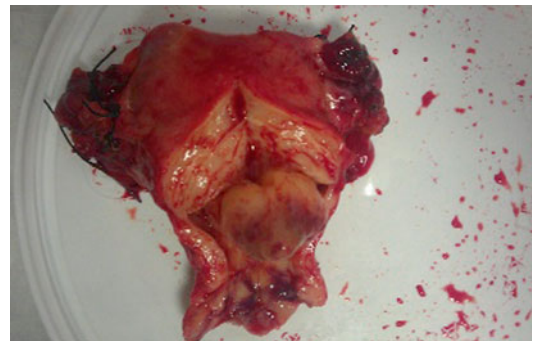

Fig. 17.23 A uterine leiomyosarcoma in a postmenopausal patient with a intramural myoma which expands into the uterine cavity, as a subserous myoma

Morcellation

Laparoscopic morcellation has been an accepted technique for removing large masses from the abdomen through small ports enhancing the value and scope of minimally invasive surgery for many years. Traditionally the morcellator was a hand held manually driven device until 1993 when the first electronic version was introduced. This significantly improved the speed and decreased the fatigue factor associated with the morcellation of large masses. There are numerous models on the market with a blade diameter ranging from 12 to 20 mm. As with any instrument the wide spread use of morcellators placed in the hands of surgeons with varied experience will result in complications. These include

damage to large and small intestine, major vascular injuries including the aorta, vena cava, mesenteric and iliac vessels. The bladder, ureters and kidneys have also been inadvertently injured as well [18].

To prevent these complications the operator must be in complete control of the instrument and maintain visual contact with the active blade and the tissue to be morcellated. A common mistake is to advance the morselator and drive it toward the tissue rather than always bringing the tissue toward the device. Entry into the abdomen with the morcellator must be controlled and pointed away form vital structures. The morcellator should always be pointed along the anterior abdominal wall away form all vital structures to prevent inadvertent activation and damage. Placement of the morcellator either in the umbilical, suprapubic or lateral wall is operator dependent but must be free of vital structures. The inadvertent loss of pneumoperitoneum must be avoided to protect the viscera. Although not a complication of the morcellator itself. Fragments of tissue left in the peritoneal cavity have been known to cause leiomyomatosis. This condition although benign in nature may manifest itself by the growth of lesions which will necessitate additional surgery. Large enough fragments left behind have been known to cause peritonitis and abscess formation. It is extremely important to examine all of the operative quadrants and remove all visible fragments of tissue [27].

Copious irrigation and suction to remove all small fragment of tissue is strongly advised. A more serious implication of tissue morcellation is the inadvertent spread of undiagnosed uterine cancer. This issue has been a focus of an FDA reevaluation of power morcellation since a patient was recently diagnosed with uterine sarcoma after tissue morcellation was employed during her hysterectomy. The FDA has taken the position to discourage the use of power morcellation for the treatment of enlarged uteri and fibroid tumors which can not be removed in toto [30].

As previously discussed the incidence of undiagnosed uterine malignancies is no greater than 1–3 per 1,000 procedures. Understanding that the definitive preoperative diagnosis of uterine sarcomas has not been established both ACOG and the AAGL are suggesting that the use of power morcellation be only used in patients with minimal risk, and should be avoided when other alternatives are available. Included in that statement is a thorough discussion with the patient about the pros and cons of power morcellation. Both organizations are working to generate more studies to identify preoperative markers of sarcomatous change [31, 32].

Preoperative gadopentatate dimeglumine-enhanced (Gd DTPA) MRI and serum total LDH and LDH isoenzymes demonstrate a low false negative predictive value, however the false positive predictive value is greater than 17 % [26].

Other options for tissue removal must be considered including mini laparotomy, colpotomy and morcellation within a surgical bag. The surgical dilemma is to provide adequate preoperative consent that clearly outlines the potential risks and utilize all diagnostic criteria available to avoid undiagnosed dissemination of cancer while still offering a minimally invasive technique to the vast majority of patients treated for benign disease.

Adenomyosis

Adenomyosis in itself isn't a complication of myomectomy however its presence and inability to remove it completely complicates the successful result of a myomectomy when the suspected adenomyosis had not been detected preoperatively. Adenomyosis is the presence of endometrial glands and stroma within the uterine musculature. The most common etiology is that it develops as a result of invagination of the basalis endometrium into the myometrium. Some studies have shown that the ectopic adenomyotic tissue does not behave the same way as eutopic endometrium and is constantly proliferating rather than demonstrating the normal cyclic apoptosis [26].

The diagnosis can be made by transvaginal ultrasound (Fig. 17.24) and MRI.

The classic ultrasonic picture is that of myometrial cysts distorted heterogeneous myometrial echotexture [29].

And poorly defined myometrial heterogeneity. MRI findings demonstrate a large asymmetric uterus without myomata. Thickening of the junctional zone

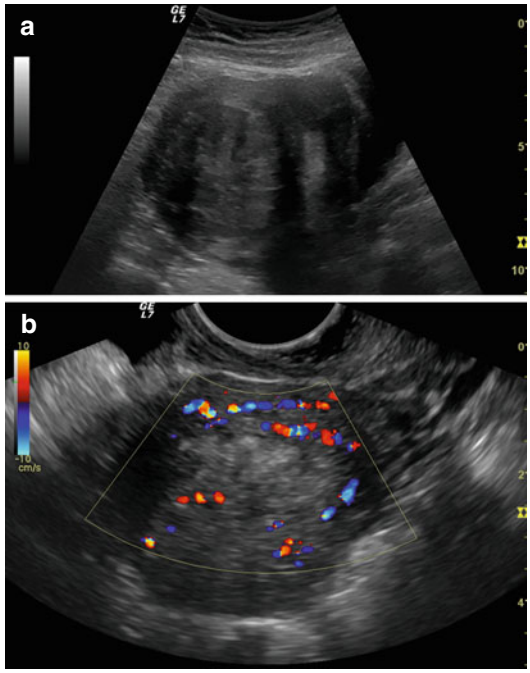

Fig. 17.24 A ultrasonographic scan of uterine adenomyoma without and with Eco Doppler scan

or an abnormal ratio between the junctional zone and myometrium [28].

The sensitivity of both techniques is compromised by the presence of myomas in the uterus. Because of the diagnostic dilemma the presence of adenomyosis at the time of myomectomy complicates the outcome of the procedure. The dissection of the adenomyoma thought to be a fibroid will not have a discrete capsule, the margins will not be clearly defined and therefore the excision will most likely be incomplete. When myomectomy is being performed for infertility and adenomyosis is encountered there is a loss of myometrial tissue which may lead to scar formation and the inability of the uterus to expand during pregnancy. the spontaneous abortion rate is 38 % higher then the general population when adenomyosis is present [10].

Pearls to Avoid Hysteroscopic Complications

1. One who scopes and walks away can always scope another day.
2. Do preoperative ultrasound and saline infusion sonogram to map leiomyoma number, size, location, and depth into myometrium.
3. Use Laminaria, Misoprostol, or Pitressin to make cervical dilation easier.
4. If possible, insert hysteroscope before cervix dilated.
5. Perforation with scissors, forceps, or active electrode warrants consideration for immediate laparoscopy or laparotomy.
6. Be familiar with the fluid pump and know limits of intravasation of conductive (2,000 ml) and nonconductive media (maximum allowable fluid absorption limit = 17.6 ml/kg × body weight kg).
7. Purge inflow line of room air prior to insertion of hysteroscope into the cervix.
8. Drop in end-tidal CO_2 or O_2 saturation is a sign of gas embolism.

Acknowledgment We greatly thank to Antonio Malvasi for his efforts in chapter illustration.

References

1. Thomas JA, Leyhland N, Duranel N, Windrim RD. The Use of oral misoprostol as a cervical ripening agent in operative hysteroscopy: a double-blind, placebo-controlled trial. Am J Obstet Gynecol. 2002; 186:876.
2. Preutthipan S, Herabutya Y. Vaginal misoprostol for cervical priming before hysteroscopy: a randomized controlled trial. Obstet Gynecol. 2000;96:890.
3. Phillips DR, Nathanson HG, Milim SJ, Haselkorn JS. The effect of dilute vasopressin solution on the force needed tor cervical dilatation: a randomized controlled trial. Obstet Gynecol. 1977;89:507.
4. Wortman M. Complications of hysteroscopic surgery. In: Isaacson K, editor. Complications of gynecologic endoscopic surgery. Philadelphia, PA: Elsevier; 2006. p. 185.
5. Jansen FW, Vredevoogd CB, Ulzen KV, Hermans J, Trimbos JB, Trimbos-Kemper TCM. Complications of hysteroscopy: a prospective, multicenter study. Obstet Gynecol. 2000;96:266.
6. Magos AL, Baumann R, Lockwood GM, Turnbull AC. Experience with the first 250 endometrial resections for menorrhagia. Lancet. 1992;337:1074.
7. Wamstecker K, Emanuel MH, deKruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: Results regarding the degree of intramural extension. Obstet Gynecol. 1993;32:736–40.
8. Corson SL, Brooks PG. Resectoscopic myomectomy. Fertil Steril. 1991;55:1041–4.
9. Brooks PG. Complications of operative hysteroscopy: how safe is it? Clin Obstet Gynecol. 1992;35:256.

10. Wortman M, Daggett A. Hysteroscopic myomectomy. J Am Assoc Gynecol Laparosc. 1995;3:39.
11. Loffer FD, Bradley LD, Brill AI, Brooks PG, Cooper JM. Hysteroscopic fluid monitoring guidelines. J Am Assoc Gynecol Laparosc. 2000;7:167.
12. Serden SP, Brooks PG. Treatment of abnormal uterine bleeding with the gynecologic resectoscope. J Reprod Med. 1991;36:697.
13. Indman PD. Hysterosocpic treatment of menorrhagia associated with uterine leiomyomas. Obstet Gynecol. 1993;81:716.
14. Itzkowic D. Submucous fibroids: clinical profile and hysteroscopic management. Aust N Z J Obstet Gynecol. 1993;33:63.
15. Munro MG, Weisberg M, Rubenstein E. Gas and air embolization during hysteroscopic electrosurgical vaporization: Comparison of gas generation using bipolar and monopolar electrodes in an experimental model. J Am Assoc Gynecol Laparosc. 2001;8:488.
16. Stoloff DR, Isenberg RA, Brill AI. Venous air and gas emboli in operative hysteroscopy. J Am Assoc Gynecol Laparosc. 2001;8:181.
17. Loffer FD. Removing intrauterine lesions: myomectomy and polypectomy. In: Bieber E J, Loffer FD, editors. Gynecologic resectoscopy. Cambridge, MA: Blackwell Science; 1995. p. 186.
18. Alessandri F, Lijoi D, Mistrangelo E, Ferrero S, Ragni N. Randomized study of laparoscopic vs minilaparotomic myomectomy for uterine myomas. J Minim Invasive Gynecol. 2006;13(2):92–7.
19. Sizzi O, Rossetti A, Malzoni M, Minelli L, La Grotta F, Soranna L, Panunzi S, Spagnolo R, Imperato F, Landi S, Fiaccamento A, Stola E. Italian multicenter study on complications of laparoscopic myomectomy. J Minim Invasive Gynecol. 2007;14(4):453–62.
20. Dubuisson JB, Chavet X, Chapron C, Gregorakis SS, Morice C. Uterine rupture during pregnancy after laparoscopic myomectomy. Hum Reprod. 1995;10: 1475–7.
21. Parker WH, Einarsson JI, Istre O, Dubuisson JB. Risk factors for uterine rupture after laparoscopic myomectomy. J Minim Invasive Gynecol. 2010;17(5): 551–4.
22. Pistofidis G, Makrakis E, Balinakos P, Dimitriou E, Bardis N, Anaf V. Report of 7 uterine rupture cases after laparoscopic myomectomy: update of the literature. J Minim Invasive Gynecol. 2012;19(6): 762–7.
23. Einarsson JI, Grazul-Bilska AT, Vonnahme KA. Barbed vs. standard suture: randomized single-blinded comparison if adhesion formation and ease of use in an animal model. J Minim Invasive Gynecol. 2011;18:528–30.
24. Tulandi T, Einarsson JI. The use of barbed suture for laparoscopic hysterectomy and myomectomy: a systematic review and meta-analysis. J Minim Invasive Gynecol. 2014;21(2):210–6.
25. Stamatopoulos CP, Mikos T, Grimbizis GF, Dimitriadis AS, Efstratiou I, Stamatopoulos P, Tarlatzis BC. Value of magnetic resonance imaging in diagnosis of adenomyosis and myomas of the uterus. J Minim Invasive Gynecol. 2012;19(5):620–6.
26. Goto A, Takeuchi S, Sugimura K, Mauro T. Usefulness of qd-DTPA contrast enhanced MRI and serum determination of LDH and its isoenzymes in the differential diagnosis of leiomyosarcoma from degenerating leiomyomata of the uterus. Int J of Gynecol Cancer. 2002;12(4):354–61.
27. Cucinella G, Granese R, Calagna G, Somigliana E, Perino A. Parasitic myomas after laparoscopic surgery: an emerging complication in the use of morcellator? Description of four cases. Fertil Steril. 2011;96(2):e90–6.
28. Garcia L, Issacson K. Adenomyosis: review of the literature. J Minim Invasive Gynecol. 2011;18(4): 428–37.
29. Shwayder J, Sakhel K. Imaging for uterine myomas and adenomyosis. J Minim Invasive Gynecol. 2014; 21(3):362–76.
30. Laparoscopic uterine power morcellation in hysterectomy and myomectomy: FDA/safety Communication April 17 2014.
31. Power morcellation and occult malignancy in gynecologic surgery ACOG special report May 2014.
32. Morcellation during uterine tissue extraction AAGL tissue extraction task force May 2014.

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