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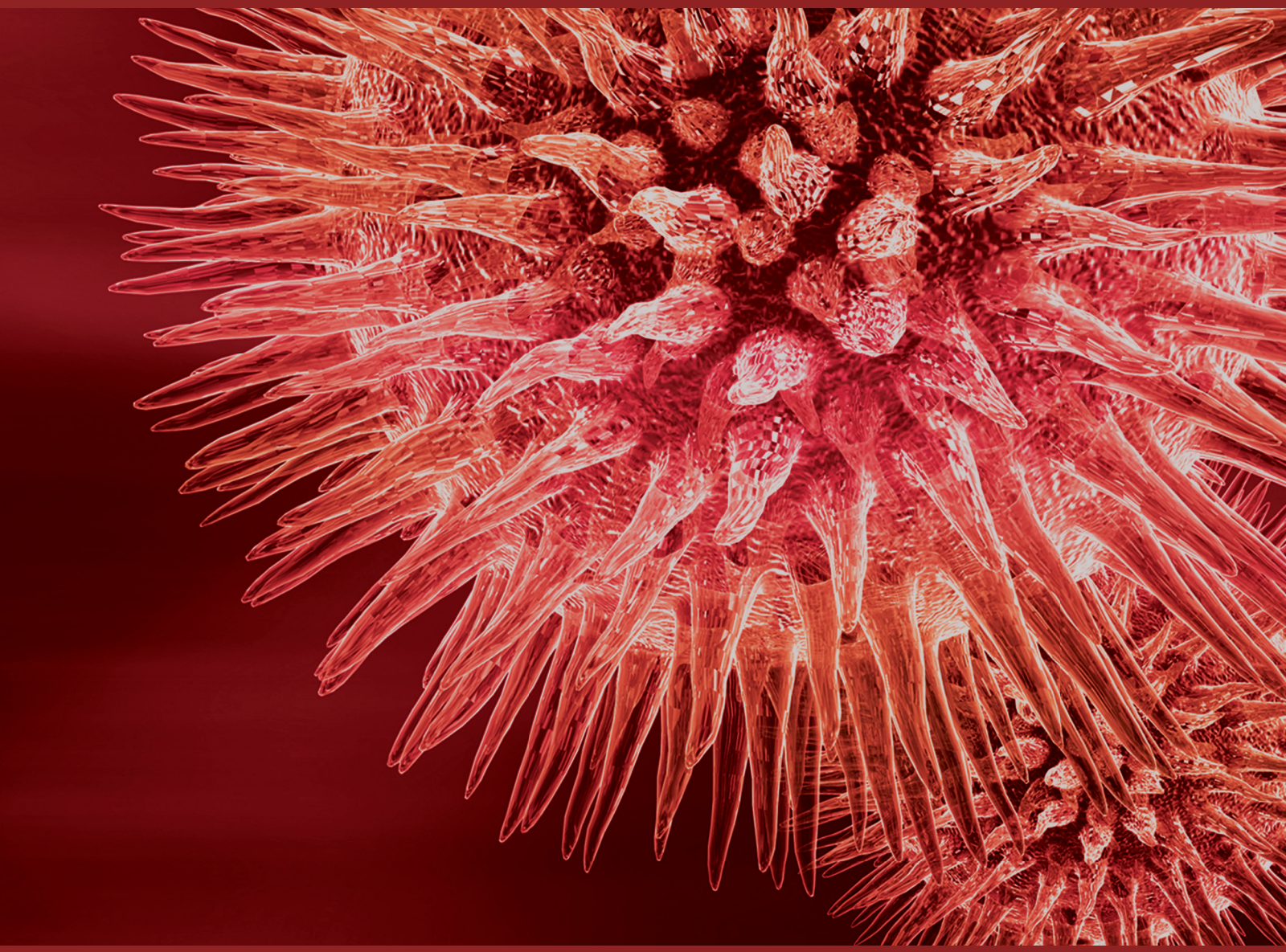
Adenomyosis and Myomata: Risks, Problems, and Complications in Diagnosis and Therapy of Adenomyosis and Myomata

Lead Guest Editor: Rudy L. De Wilde
Guest Editors: Markus Wallwiener, Attilio S. Sardo, Vasilis Tanos, and Sven Becker



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Editorial

Adenomyosis and Myomata: Risks, Problems, and Complications in Diagnosis and Therapy of Adenomyosis and Myomata

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The goal of this special issue is to address research concerning risks and problems related to the diagnosis and therapy of adenomyosis and myomata. During the last years, there have been several controversies in the scientific community regarding these topics. The original papers gathered in this special issue highlight and inform the readers about the innovations made in this field.

The complex pathogenesis shows that there are multiple biogenetical and multifactorial aspects influencing the etiology and growth of myomata. Furthermore, the existence of adenomyosis seems to be coupled with molecular differences in myometrial receptors. One of the examples here is the significant increase in GPER expression in case of adenomyosis (J. Li et al.).

Predictive factors that point towards adenomyosis in a clinical set-up make the necessary differential diagnosis between a myoma and an adenomyoma possible. Combining clinical history and symptoms, gynecological examination and MRI (H. Krentel et al.), and sonographical aspects (V. H. Eisenberg et al.) enhance the certainty in the decision-making process. The impact on the reproductive outcome and influence on endometrial receptivity, embryo implantation, and possible "embryotoxicity" as well as anatomical distortion may interfere throughout the duration of pregnancy and affect the obstetrical outcome (N. F. Vlahos et al.).

Hysteroscopy offers the advantage of visualization of the uterine cavity, giving the option of collecting histological samples under visual control. Possibilities of obtaining diagnostic criteria and performing transcervical treatment in selected cases are also discussed (A. Di Spiezio Sardo et al.). The hysteroscopic morcellation of submucous myomata seems feasible, even in cases of a location in the uterine wall of more than half of the tumor (S. G. Vitale et al.).

Myomas affect, with some variability, all ethnic groups and nearly 50% of all women during their lifetime. While some remain asymptomatic, significant and sometimes life-threatening problems can occur. In most cases surgical therapy cannot be avoided: hysteroscopic or laparoscopic therapy is the gold standard (A. El-Balat et al.).

Apart from the routine surgically induced complications, especially in myomata and adenomyosis, there is a risk of injury to the close by organs and a possibility of tissue spilling causing parasitic myoma, endometriosis, or sarcoma spreading (V. Tanos et al.). Possibilities to avoid this tumor spilling by contained in-bag morcellation with description of bag-related application techniques are reported (S. Rimbach et al.).

Nonsurgical alternatives by high-intensity focused ultrasound, eventually combined with oxytocin administration (T. Lozinski et al.), and GnRH-agonists and antagonists have

been used in the treatment of symptomatic uterine fibroids with long-lasting effects (M. Safrai et al.). Selective progesterone receptor modulators add perspectives and open new medication-based treatment options (T. Rabe et al.). In all continuously applied medications, not only early drug related complications, but also problems due to the total dosage of the medication should be taken into account.

As this special issue deals with the most frequent diseases treated by gynaecologists, it clearly should be seen as a further step to engage in research and optimizing treatment modalities. The authors, as key opinion leaders in their field, have shared their thoughts and knowledge with only one purpose: to reach a next level in the standard of care dealing with myomata and adenomyosis.

Acknowledgments

The guest editors would like to thank all the authors, who contributed to this special issue. This high quality publication would not have been possible without the participation of the expert reviewers, who provided feedback and criticism throughout the review process.

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Clinical Study

Oxytocin Administration in High-Intensity Focused Ultrasound Treatment of Myomata

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Objectives. The aim of the study was to evaluate the clinical efficacy of magnetic resonance-guided High-Intensity Focused Ultrasound (HIFU) in patients with symptomatic uterine fibroids (myomata) after application of oxytocin. *Methods*. 156 women with symptomatic uterine fibroids were treated using MR-guided HIFU procedure. 51 patients had additional IV administration of 40 IU of oxytocin in 5% Glucose or 0,9% NaCl solution during therapy. Before and after the procedure we performed MR and measured initial perfused volume, final perfused volume, nonperfused volume (NPV), and treated volume ratio (TVR). The follow-up was up to 15 months to assess efficacy of treatment and relief of symptoms. *Results*. Nonperfused volume was statistically significantly larger in oxytocin group than in control group (p=0.0019). The remaining parameters did not show significant difference between both groups. *Conclusion*. Oxytocin administration seems to improve efficiency of HIFU therapy although further research is required to assess its value. This study' clinical registration number is DRKS00014794.

1. Introduction

The uterine fibroid (also known as fibromyoma or myoma) is the most common benign disease in women [1–3]. Symptoms caused by fibroids, e.g., heavy bleeding, anemia, pain, increased size of the abdomen, and specific fertility and pregnancy complications, are major causes of morbidity in women in reproductive age. They occur in at least 40% of all women and account for significant healthcare and social costs due to surgical treatment (mainly hysterectomies) and subsequent absence at work [4]. The presence of fibroids can lead to decrease of fertility due to impairment of endometrial receptivity and abnormal implantation of the blastocyst. It has been suggested that fibroids may also disrupt normal myometrial peristaltic movements impeding sperm arrival at the fallopian tubes and embryo transport into the uterus [5, 6].

The fibroids can be classified by as subserosal, intramural, or submucosal depending on their location in the uterus. Pedunculated fibroids arise from either the serosal surface or from the mucosal surface. Histologically they are benign, hormone-sensitive smooth-muscle tumors containing fibrous connective tissue. They are demarcated from the surrounding uterine tissue by a pseudocapsule. Fibroids can undergo hyaline degeneration or hemorrhagic infarction. After menopause they regress and may calcify [3].

The purpose of the fibroid treatment is relief of symptoms such as pain and bleeding. There are many therapeutic methods available. Historically first- and last-line therapy was a surgical procedure: myomectomy or hysterectomy. Myomectomy can be associated with penetration to the uterine cavity that induces adhesion, subsequently leading to a decrease in fertility. Hysterectomy causes irreversible sterilization. The presence of uterine fibroids is the most

common indication for hysterectomy in the United States [4]. Operative treatment is still gold standard for symptomatic fibroids. Each case should be considered very carefully based on individual variables. Optimal treatment depends on age, symptoms, parity, and further reproductive plans. Many patients are afraid of surgery and its consequences and want to avoid or even decline this method of treatment. Unfortunately, alternative treatment options are very limited.

Medical therapy is essentially a treatment option for the control of symptoms including reduction in fibroid volume and in menstrual blood loss. Oral contraceptive pills administration decreases symptoms such as pain and bleeding but no pharmacological agent is curative of fibroids. Unfortunately OTC does not work in a certain population of patients, so this option is limited even as a symptom relief treatment. GnRH analogues have been most commonly used drugs. Recently new agents have shown promising effects in symptom improvement and fibroid regression, like aromatase inhibitors, mifepristone, selective estrogen receptor modulators, and selective progesterone receptor modulators. They do not cause hypoestrogenic symptoms associated with GnRH analogues [5].

Less invasive procedures such as laser therapy, artery embolization, and cryoablation are safer than surgical treatment but unfortunately they also have certain limitations. Laser ablation of fibroids can be performed though laparoscopic or endoscopic route or using percutaneous approach under the magnetic resonance (MR) guidance. Interstitial laser photocoagulation, with low-power laser guided by thermal monitoring, is used to destroy the fibroid tissue. A 1064 nm wavelength laser is applied to ensure sufficiently deep penetration into the fibroid tissue. Laparoscopic or hysteroscopic laser ablation has been shown to decrease fibroid volume by 50%–70% [7]. Cryotherapy can be applied through laparoscopic or hysteroscopic approach. Low temperature is obtained by rapid freezing using high-pressure gas. Side effects of this procedure are infection end fever [2]. Radiofrequency ablation is used through laparoscopy or hysteroscopy. The drawback of this technique is the lack of possibility of monitoring the local temperature in the threated tissue [2].

MR-guided High-Intensity Focused Ultrasound (HIFU) procedure is a noninvasive option of fibroids therapy. In 1942, Lynn et al. proposed the use of Focused Ultrasound (FUS) to achieve thermal effect in tissue. Device to treat neurologic disorders such as Parkinson's diseases was created in 1950 by Fry Brothers [8]. A research about utility of MR-HIFU for another disease has taken many years. At the beginning in 21st century uterine fibroids started to be treated by ultrasound beam [7]. InSightec Exablet system 2000 received FDA approval in 2004 for fibroids treatments. Up to now, many patients with symptomatic fibroids were treated. This method of conservative treatment of symptomatic uterine fibroids has been reported to be effective and safe [9]. Another system that has been approved in Europe is Sonalleve MR-HIFU (Philips Healthcare, Andover, MA, USA).

MR-controlled ultrasound beam causes heating of the tissue and temperature-related protein denaturation in the tumor tissue. Clinical symptoms of fibroids lessen relatively quickly but decrease of fibroid volume takes much more time. [9]

Table 1: Types of fibroids according to FIGO classification [13].

FIGO type	1	2	3	4	5	6
Oxytocin group (N=51)	6	1	21	11	7	5
Control group (N=105)	9	5	36	22	16	17

2. Objectives

The aim of the study was to assess the influence of supplementary IV oxytocin administration on HIFU treatment in women with symptomatic uterine fibroids. The application of MR-HIFU therapy is limited to certain group of patients, depending on the type of fibroids, their localization, and positive qualification based on MR criteria. [9, 10]

In our clinical practice, in open surgery and laparoscopic procedures, we observed beneficial effects of in- and post-surgery oxytocin administration, e.g., less bleeding and shorter time of Douglas pouch catheter drainage. Other researches reported similar to observations. [11, 12]

3. Material and Methods

156 women with symptomatic uterine fibroids were enrolled to this study between September 2016 and June 2017. In 2016 we did not use oxytocin. We started recruiting consecutive patients to the oxytocin group from the beginning of 2017. There were no differences including and excluding factors in both groups of patients. Each patient was counseled about potential risks and side effects of oxytocin and signed informed consent form.

Types of fibroids according to FIGO classification are shown in Table 1 [13].

Willingness to preserve fertility, history of pregnancy loss, and infertility associated with fibroids were main inclusion criteria. We also included asymptomatic patients with fibroids that were not able to conceive spontaneously for more than 12 months and/or with history of miscarriages. Other inclusion criteria were as follows: age 20-43 years (mean 36.3), symptomatic fibroid or fibroids (≤2), and positive MR qualification (Funaki type I or II, suitable beam window). Mean BMI was 23.2.

Exclusion criteria were as follows: standard contraindications for MR imaging, age >43 years, and unwillingness to preserve fertility.

All patients were treated using MR-guided HIFU procedure with Sonalleve MR-HIFU (Philips Healthcare, Andover, MA, USA). HIFU was performed in Specialist Hospital Pro-Familia, Rzeszow.

The ultrasound beam has to have an unobstructed access to the fibroid. If the bowel loops were in front of the uterus it was necessary to change position of the bowel by filling the bladder with saline solution and/or the rectum with ultrasound gel. Otherwise it would not be possible to perform the procedure [14]. The amount of subcutaneous fatty tissue is

Table 2: MR parameters in both groups.

	Oxytocin group (N)	Control group (N)	Oxytocin group	Control group	t	df	p
Mean fibroid volume (mL)	51	105	87.31	90.84	0.201	154	0.8411
NPV (%)	51	105	76.2	62.8	-3.153	154	**0.0019**
Mean fibroid volume change (%)	15	39	51.7	38.2	-1.659	52	0.103

also a very important factor. The distance between the tumor and skin should not be more than 13 cm [14, 15].

In the oxytocin group there were 51 patients and 105 in the control group. In the first group 40 IU of oxytocin diluted in 500mL of 5% glucose or 0,9% NaCl was administered during the whole procedure by IV catheter at the rate of 5mL/min. Every 30 minutes blood pressure and heart rate measurements were taken and no differences were found as compared to the control group. Patients reported no complaints. No side effects were reported after oxytocin administration.

Before the procedure MR was performed to measure mean fibroid volume and initial perfused volume (IPV). Right after the procedure treated volume ratio (TVR) and final perfused volume (FPV) were assessed on MR, and subsequently nonperfused volume (NPV) was calculated (NPV=FPV-IPV). At follow-up MR scan 6 months after the procedure mean fibroid volume change was measured.

After checking for the normality of the data distribution, the *t*-test was performed to determine if the results are significantly different from each other in both groups. The difference was considered statistically significant if p-value was <0.05. Statistical analyses were done using Statistica Software (Version Stat Soft. Inc., Tulsa, OK, USA).

Ethical Approval was received from Local Ethics Committee (Polish Medical Chamber, Rzeszow Department). Clinical registration number is DRKS00014794, URL: https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00014794.

4. Results

Average time of the whole treatment was 220 min, time of sonication 111 min, 60 s, and patient's preprocedure preparation such as obtaining optimal position, filing the bladder, and/or the rectum another 80 minutes. Average volume of fibroids was 90 ml.

T2-weighted hypointense fibroids showed a frequency of 93.6%; isointense and hyperintense fibroids had frequencies of 5.60% and 1.1%, respectively. There was a negative correlation between NPV and age (r = -0.083, p = 0.307) and treatment time (r = -0.253, p = 0.001). Median TVR was 96.0 % in small and 76.5 % in large fibroids.

We found a significant difference in NPV that was larger in patients with oxytocin administration during HIFU therapy (Table 2 and Figure 1). No significant difference was found in mean fibroid volume (Table 2 and Figure 2). Mean fibroid volume change (Table 2 and Figure 3) was larger in the oxytocin group but the difference was not statistically significant possibly due to small number of patients with this parameter assessed at follow-up (15 versus 39).

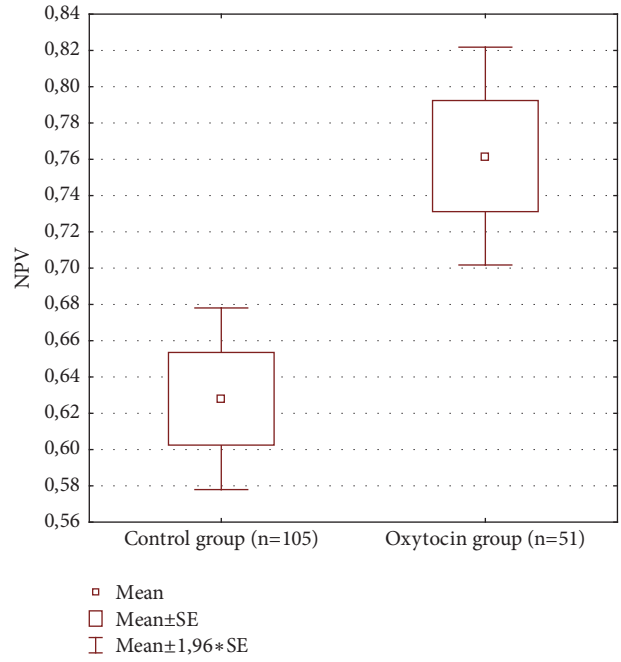

Figure 1: Nonperfused volume (NPV) in both groups.

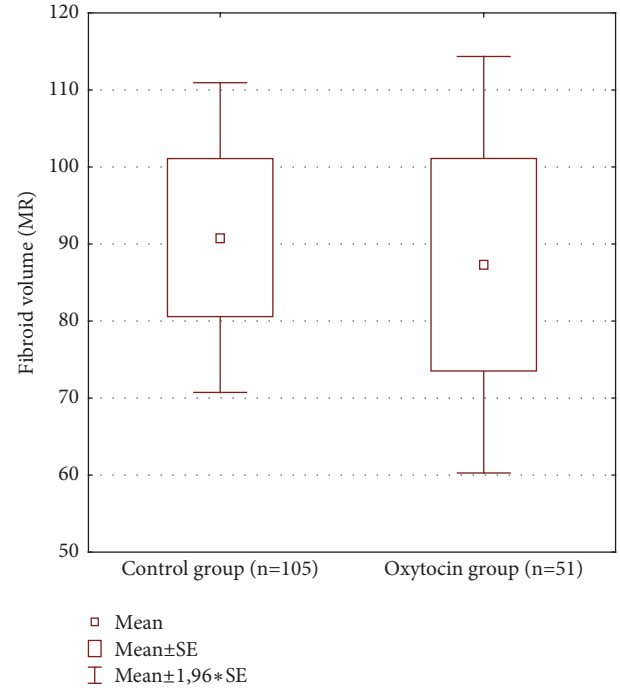

Figure 2: Fibroid volume in both groups.

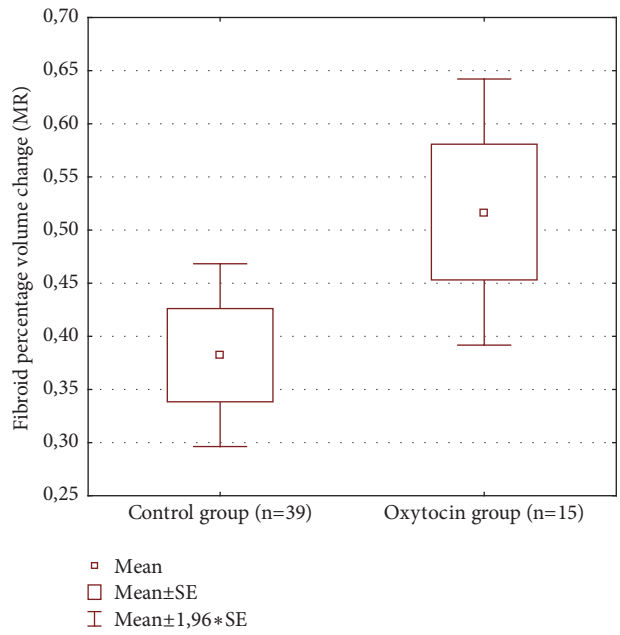

Figure 3: Fibroid volume change in both groups.

5. Discussion

Oxytocin is nonapeptide hormone released by the hypothalamus, causing contractions and involution of the uterus and closure of uterine blood vessels after delivery. Estrogens act synergistically with oxytocin. Stimulation of receptors situated on the cervix and nipples induces release of oxytocin. Application of oxytocin is widespread in the world in induction of labor. It was believed that oxytocin does not have an effect on nonpregnant uterus, because there are no detectable oxytocin receptors in the myometrium. However high-dose oxytocin infusion during myomectomy decreases blood loss during the procedure [11, 12]. This is consistent with our observation of decreased blood loss after oxytocin administration during laparoscopic and open surgery myomectomy alike. This data will be published soon.

We found that NPV (nonperfused volume) was significantly larger in patients with oxytocin administration during HIFU therapy. Also the mean fibroid volume change (decrease of volume as measured in MR) was noticeable but the difference has not reached the level of statistical significance, possibly due to a small number of patients with this parameter assessed (15 in oxytocin group versus 39 in control). This requires further research with follow-up in larger group of patients.

Our data suggests that oxytocin has some effect for nonpregnant uterus. Contraction of uterine muscle and blood vessels decreases blood flow and that may lead to better results in HIFU therapy. Funaki found that efficiency of HIFU depends on vascularity and flow in tumor [10].

The practical consequence of oxytocin administration during HIFU was an increase of efficiency of the HIFU treatment. NPV is a parameter quantifying the degree of necrosis after treatment. Therefore measurement of NPV allows assessing effectiveness of the treatment. Our results showed that NPV was significantly better after oxytocin administration.

It could be hypothesized that oxytocin causes contraction of the fibroid leading to externalization of extracellular fluid and, as a result, more effective heating of the tumor tissue by the ultrasound beam. An increase in the blood flow in the fibroid tissue decreases the efficiency of HIFU treatment. This phenomenon is known as a "cooling effect". We suspect that oxytocin administration decreases this effect due to vasoconstriction; hence heating of the tumor tissue is increased [16]. Similar observation about the oxytocin effect during MRgFus was first reported by Zhang et al. [17].

The average duration of the MF-HIFU is longer than the surgical treatment, but from our experience no patient considered it as a drawback. Zhang observed shorter duration of the procedure and better NPV in patients stimulated by oxytocin during treatment of adenomyosis [17]. Jeong reported the same observations in patients with fibroids [18].

6. Conclusions

Intravenous administration of oxytocin during MR-HIFU therapy may potentially improve efficiency of fibroid treatment. However it still requires further research.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Research Article

Selective Progesterone Receptor Modulators for the Medical Treatment of Uterine Fibroids with a Focus on Ulipristal Acetate

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Uterine fibroids are the most frequent benign tumours in women of child-bearing age. Their symptoms are diverse and the quality of life of the women affected can be significantly impaired. While treatment to date has been primarily by means of surgical intervention, selective progesterone receptor modulators (SPRMs) open up new medication-based treatment options. EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recently completed its review of ESMYA® (ulipristal acetate, 5 mg), following reports of serious liver injury, including liver failure leading to transplantation in postmarketing settings. We will provide some information on the PRAC's recommendations to minimize this risk. Nevertheless, the effectiveness and safety of the SPRM ulipristal acetate (UPA), both with regard to preoperative administration and with regard to an intermittent administration as long-term treatment for patients with symptomatic uterine fibroids, have been shown in several clinical studies (PEARL I–IV).

1. Introduction

Uterine fibroids (synonym, leiomyomata) are benign tumours originating from the smooth musculature of the uterus, the myometrium. They consist of smooth muscle cells and fibroblasts, which are embedded in the abundant extracellular matrix and can reach a considerable size. They grow intramurally, in the subserous or in the submucous layer, and are classified into 8 different types [1].

1.1. Clinical Symptoms. Fibroids occur in women of child-bearing age and may lead to a significant limitation of their quality of life [2]. The clinical symptoms include menstrual disorders (e.g., hypermenorrhea, menorrhagia, and dysmenorrhoea), right up to anaemia. The increase in the size of the uterus can lead to gastrointestinal symptoms (e.g., obstipation), voiding disorders (e.g., residual urine, nocturia, and pollakisuria), and pain or a sensation of pressure in the pelvic or abdominal region. Further possible manifestations are fertility disorders or recurrent miscarriages. Patients with fibroids, however, may also have no medical complaints at all [3, 4].

1.2. Risk Factors. Age and ethnicity are the most important risk factors for the occurrence of fibroids. No fibroids have been described in prepubescent girls to date. Fibroids first develop during adolescence, with increasing incidence until menopause. In the USA, an incidence of uterine fibroids in women of African ancestry, increased by two to three times in comparison with Caucasian women, has been observed [5]. Nulliparity, early menarche, a history of dysmenorrhoea, a family history of fibroids, genetic factors, and a high body

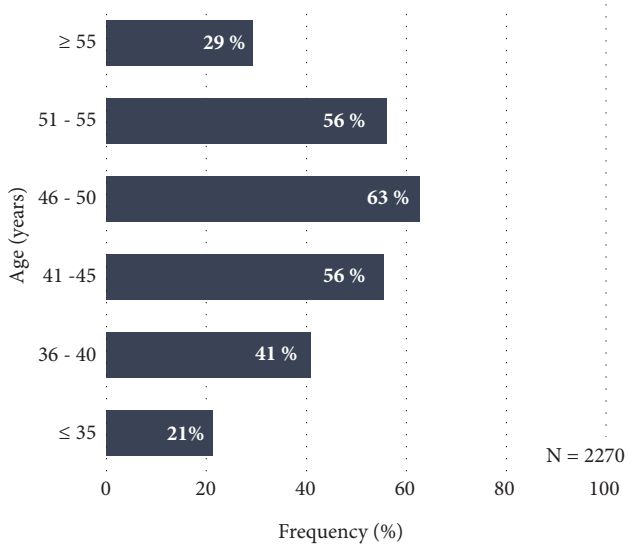


Figure 1: Prevalence of fibroids according to age-group, as percentages (N = 2,270), according to Ahrendt et al. [7].

mass index (BMI) have been mentioned as further possible risk factors. The risk can also be increased by hypertension and diabetes [4–6].

1.3. Epidemiology. Fibroids are the most frequent benign, solid tumours of the female genital tract [7]. In a prospective study of the prevalence of fibroids in Germany, Ahrendt et al. describe the data of 2,296 women who visited out-patient gynaecology facilities and were not less than 30 years of age [7]. Fibroids were detected in 41.6% of the women by means of transvaginal sonography. Age-dependence was able to be demonstrated. With increasing age, the prevalence of the fibroids in premenopause increased from 21.3% (30 – 35 years of age) to 62.8% (46 – 50 years of age). The prevalence declined again in patients over 50 years of age. In patients over 55 years of age, these reached a value of 29.4% (Figure 1).

In this study, the occurrence of fibroids did not correlate either with the age at menarche or with the body mass index. Due to their results, the authors assume that more than 40% of the women over 30 years of age suffer from fibroids and that more than 50% of women in Germany develop uterine fibroids at some time in their lives.

1.4. Pathogenesis. To date, the exact pathogenesis of uterine fibroids is largely unexplained. Thus far, aside from sexual hormones, genetic and epigenetic factors, cytokines, chemokines, and components of the extracellular matrix have been linked with the occurrence of fibroids [4]. More recent studies suggest that not only oestrogen but, in particular, progesterone plays an important role in the occurrence and growth of fibroids.

According to Kim and Sefton [12], not only does the mode of action of progesterone involve classic nuclear receptor effects on gene regulation, but there are also indications that the progesterone receptors (PR) directly activate signal pathways, interact with growth factor signal systems, and hence promote the proliferation and viability of fibroids.

1.5. Therapeutic Options. Due to the clinical symptoms, such as severe bleeding, pain in the pelvic region, and infertility, treatment is required in approximately a third of patients with uterine fibroids [4]. According to Stewart et al. [5], only few randomised controlled studies have been performed so far, which compare the effectiveness of various treatment techniques with one another and take variables such as age, ethnicity, and the characteristics of the tumour into consideration at the same time. In addition to various surgical techniques (e.g., hysterectomy or organ-preserving minimally invasive procedures) and radiological-gynaecological therapeutic techniques (e.g., uterine artery embolisation (UAE) and magnetic resonance imaging-guided focused ultrasound (MRgFUS)), medication-based treatment strategies are also possible therapeutic options. The current therapeutic options, including their advantages and disadvantages, have been described in detail in the publication by Rabe et al. [2].

Criteria which should be considered in the selection of the most suitable treatment are the patient's chronological age, the patient's wish to retain her organ and/or fertility, as well as tumour-associated factors such as the number, size, and location of the fibroids [4].

Many therapeutic options for fibroid patients involve surgical interventions; approximately a third to half of all hysterectomies are due to fibroids [5].

Consequently, there is a great need to develop new and effective therapeutic alternatives for women, in which organ retention and the retention of fertility have the priority. In these cases, a medication-based treatment is suitable. GnRH agonists, which trigger a temporary menopause with amenorrhoea by means of a reduction in the progesterone and oestrogen levels and therefore lead to an increase in the haemoglobin level, are increasingly more seldom employed therapeutically; their administration also leads to a reduction of the size of the fibroids. GnRH agonists are used preoperatively. Because of their side-effect profile, with climacteric complaints and reduced bone density, however, they can only be used over a brief period [4, 13]. As well, the targeted reduction of the uterine or fibroid volume is relatively quickly reversible after discontinuing the medication [13]. Another class of substances is the selective progesterone receptor modulators (SPRMs). One representative of this class is ulipristal acetate (UPA), which was approved in 2012 for the preoperative treatment of moderate to severe symptoms due to uterine fibroids in adult women of child-bearing age. Ulipristal acetate was also approved in May 2015 for intermittent treatment and it therefore presents a fully fledged alternative to a surgical procedure.

2. Selective Progesterone Receptor Modulators (SPRMs)

SPRMs are a substance class of synthetic steroids which have agonistic and/or antagonistic effects on the progesterone receptors (PR). Because of their structural similarity to progesterone, they are able to be taken up by its receptors and,

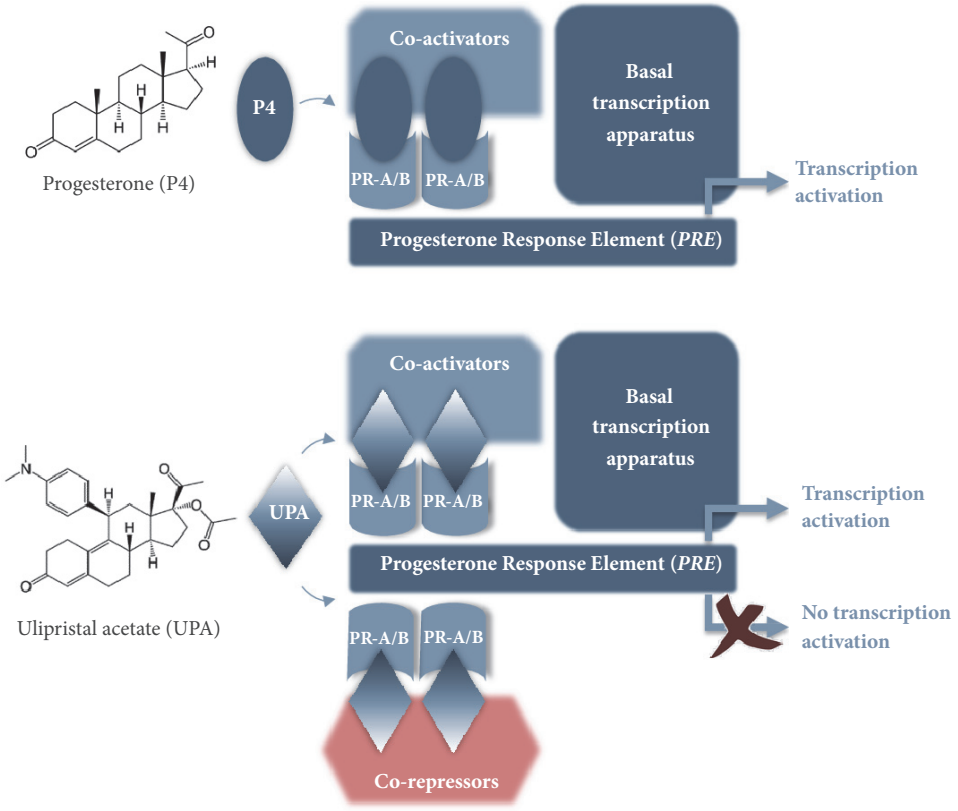


Figure 2: Mode of action of SPRMs according to Bouchard et al. [8]: SPRMs interact with coactivators and corepressors. In this way, the gene transcription is either inhibited or activated. This means that the stimulating or inhibiting effect of an SPRM is dependent on its chemical structure.

depending on the change in the conformation of the receptor resulting from the bond, corepressors or coactivators are accumulated in the corresponding binding domain. Whether an SPRM has a more agonistic or antagonistic effect depends on its structure and the change in the conformation of the progesterone receptor and on the availability of coregulators (ratio of coactivators to corepressors) in a particular cell type (Figure 2). The activity of an SPRM is also affected by the tissue type and cell type, as well as the physiological context (e.g., pregnancy) [8, 14].

Unlike GnRH agonists, which only affect the pituitary gland, where they cause a downregulation and a desensitisation of the GnRH receptors with a consecutive decrease in serum estradiol and progesterone levels, SPRMs have direct effects on the pituitary gland, the fibroid, and the endometrium [4] (Figure 3). Amenorrhoea is induced by means of the direct effect on the pituitary gland, by inhibiting ovulation (in approximately 80% of patients) and simultaneously maintaining the estradiol level in the mid-follicular range [15]. The direct effect on the endometrium is expressed as a suspension of uterine bleeding and in benign reversible changes to the endometrium (PAEC: *Progesterone Receptor Modulator Associated Endometrial Changes*) and in reversible endometrial thickening. In addition, SPRMs produce a reduction in the fibroids by inhibiting the cell proliferation and by inducing apoptosis [4].

3. Ulipristal Acetate (UPA)

ESMYA® (ulipristal acetate, 5 mg) is used to treat moderate to severe symptoms of uterine fibroids.

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the benefits and risks with ESMYA®, following of serious liver injury, including liver failure leading to transplantation. The review of ESMYA® was initiated at the request of European Commission on 30 November 2017, under Article 20 of Regulation (EC) No 726/2004. The review was being carried out by the PRAC, the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. On 8 February 2018, while the review was ongoing, the PRAC issued temporary measures to protect patients' health. On 19 February 2018 a so-called "Dear Doctor Letter" ("Rote-Hand-Brief") [16] has been sent out to all gynaecologists, hepatologists, general practitioners, and pharmacies in Germany.

EMA's PRAC has completed its review of ESMYA® in May 2018. After considering all the evidence, the PRAC concluded that the medicine must not be used in women with liver problems and that certain other patients may start new treatment courses provided they have regular liver tests.

The PRAC has concluded that ESMYA® may have contributed to the development of some cases of serious liver injury. In 8 cases of serious liver injury, a role of ESMYA® in contributing to these cases is possible. It is estimated that

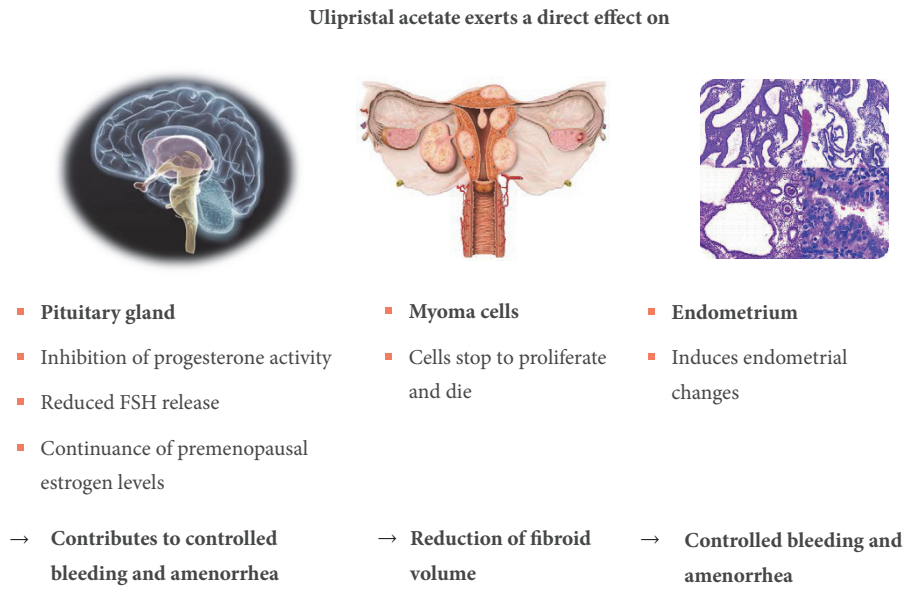


Figure 3: Effects of ulipristal acetate on the pituitary gland, endometrium, and fibroid according to Donnez and Dolmans [4].

around 765,000 patients have been treated with ESMYA® to date. The Committee has therefore made the following recommendations to minimize this risk:

(i) **ESMYA® must not be used in women with known liver problems.**

(ii) **A liver function test should be performed before starting each treatment course** and treatment must not be started if liver enzyme levels are more than 2 times the upper limit of normal.

(iii) **Liver function tests should be performed once a month during the first two treatment courses and two to four weeks after stopping treatment.** If the test is abnormal (liver enzyme levels more than 3 times the upper limit of normal), the doctor should stop treatment and closely monitor the patient.

(iv) ESMYA® should be used for more than one treatment course only in women who are not eligible for surgery. Women who are about to have surgery should continue to use only one course.

(v) A card will be included in the box of the medicine to inform patients about the need for liver monitoring and to contact their doctor should they develop symptoms of liver injury (such as tiredness, yellowing of the skin, darkening of the urine, nausea, and vomiting).

On February 2018, while the review was ongoing, the PRAC had issued temporary recommendations that no new patients should be started on ESMYA®. Having finalized its review, the Committee has now concluded that new patients can start treatment in line with the above recommendations to minimize the risk of liver injury. The PRAC's recommendations will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP) for the adoption of EMA's final opinion, and this will then go to the European Commission for a final legal decision. A letter will be sent to doctors to inform them of the new restrictions of use, which will become applicable after a Commission decision is issued. More information on the review procedure and recommendations can be found at the homepage of the EMA [17].

The clinical efficacy and safety of ulipristal acetate (UPA), both with regard to preoperative administration and with regard to an intermittent administration as long-term treatment for patients with symptomatic uterine fibroids, have been shown in several clinical studies (PEARL I–IV) as we will discuss in the following paragraphs. In patients suffering from heavy menstrual bleeding associated with uterine fibroids, repeated 3-month treatment courses with ulipristal acetate provide a medical alternative to surgery and have the potential to reduce the need for surgical intervention. No signal of hepatic toxicity was identified during the nonclinical or clinical trials of ESMYA®.

The following effects of the SPRM ulipristal acetate (UPA) have been described:

(i) **Fibroids:** the inhibition of proliferation, induction of apoptosis, and reduction of the extracellular matrix, probably due to an increased expression of metalloproteinase- (MMP-) 2, result in a reduction of the fibroids [18].

(ii) **Pituitary gland:** an inhibition or delay of the ovulation with partially reduced LH, FSH, and estradiol levels within the physiological range (60 – 150 pg/ml, mid-follicular range) result in bleeding control without the appearance of the symptoms of an oestrogen deficiency [19].

(iii) **Endometrium:** in most women, the interaction with endometrial progesterone receptors results in amenorrhoea and hence bleeding control [19, 20].

Under treatment with an SPRM, a thickening of the endometrium, which can be detected by ultrasound, may appear. This, however, does not represent an endometrial hyperplasia. This effect is asymptomatic and is reversible once the treatment has ended and menstruation has recommenced. In most cases, this endometrial thickening is caused by substance class-specific changes to the endometrium, which are referred to as PAEC (PAEC: *Progesterone Receptor Modulator Associated Endometrial Changes*) [14]. PAEC represent a distinct histological entity, which is viewed as benign and completely reversible [21, 22]. An inactive, weakly proliferating epithelium with asymmetry of the stromal and epithelial growth, which results in prominent cystically enlarged endometrial glands, which simultaneously exhibit the epithelial effects of oestrogen (mitotic) and gestagen (secretory), is characteristic of PAEC. Further characteristics are an apparently inactive and mitotically less active (weakly proliferating) endometrium, increased apoptosis in the glandular epithelium, and a compact stroma [14].

3.1. Clinical Evidence of Effectiveness

3.1.1. Preoperative Application. UPA was approved for the preoperative treatment of moderate to severe symptoms due to uterine fibroids in adult women of child-bearing age in February 2012. The evidence of effectiveness for this indication is based on the PEARL I and PEARL II studies [11, 23]. The results of these studies are shown in Table 1. The objective of the PEARL I study was to examine the effectiveness and tolerance of UPA in doses of 5 mg per day and 10 mg per day in comparison with a placebo in women with symptomatic uterine fibroids prior to scheduled surgery. All patients were given 80 mg of depot iron(II)-sulphate per day during the treatment. PEARL II is a noninferiority trial for the verification of the effectiveness of UPA versus the GnRH agonist, leuprolide acetate, in terms of the reduction of increased uterine bleeding in fibroid patients, for whom surgery had been scheduled.

In these studies, it was evident that bleeding due to fibroids was attenuated or ceased in over 90% of the patients thanks to the administration of UPA. The amenorrhoea rate under treatment with 5 mg and 10 mg of UPA was between 73% and 89%. In PEARL I, correction of the anaemia (Hb > 12 g/dl) was achieved more frequently under UPA than under the placebo (85 – 89% versus 77%) [14, 23].

Bleeding control was more rapidly achieved under UPA than with the GnRH agonist. Under UPA, amenorrhoea appeared after 5–7 days (median) and only after 21 days under leuprolide acetate [11]. According to Donnez et al. [9], 80% of the patients in both studies showed a clinically relevant reduction of > 25% of the volume of the fibroids; in 50% of the women, the fibroid volume decreased by 50%. In both UPA treatment groups, the estradiol level was in the mid-follicular range, while, for the patients treated with leuprolide acetate, this fell to postmenopausal levels [14]. Hot flushes appeared significantly more frequently under GnRH treatment. In one group of the women who did not undergo surgery following the completion of the study, it was observed that the fibroid reduction achieved under UPA persisted for up to 6 months after the completion of the study, while, in the women treated with the GnRH agonist, fibroid growth restarted quickly [11, 14]. A further study, PEARL III, was initiated on the basis of these results in order to investigate the effectiveness and safety of intermittent long-term treatment with 10 mg of UPA per day, each for 12 weeks, for the treatment of symptomatic uterine fibroids.

3.1.2. Repeated Intermittent Treatment. PEARL III [24] was an open study, in which a double-blind 10-day administration of norethisterone acetate (NETA) or a placebo followed each 12-week treatment interval with UPA (daily dose: 10 mg). Up to a total of four treatment intervals with UPA were possible. The objective of this multicentre clinical phase III study was to investigate the clinical effectiveness and safety of intermittent long-term treatment with UPA. The results of this study show that the repeated application of UPA can maximise its potential benefit in terms of bleeding control and fibroid reduction [9, 14]. In less than 10% of patients, transient endometrial thickening appeared following each treatment interval. Hyperplasias or adenocarcinomata of the endometrium were not observed at any point in time [24]. The administration of NETA after each UPA treatment interval had no effect on the size of the fibroids or on the histology of the endometrium. The most important results of PEARL III are outlined in Table 1. At this point, a detailed account of the results is dispensed with since the 10 mg per day dose for the treatment of fibroids is not approved in Germany.

In the latest PEARL IV study, the effectiveness and safety of UPA were investigated in 4 consecutive 12-week treatment intervals [10, 25]. A 3-month therapy-free follow-up was performed after each treatment interval. PEARL IV was a double-blind randomised study, in which the patients were given treatment with UPA in a daily dose of 5 mg or 10 mg. The treatment commenced within the first four days of menstruation, the next treatment interval started only with the commencement of the 2nd bleeding after the conclusion of the previous treatment interval. In total, 451 fibroid patients with severe bleeding were included in the study, of whom 228 were given a daily dose of 5 mg and 223 were treated with 10 mg of UPA. The primary effectiveness criterion was the percentage of the patients with amenorrhoea (definition: ≤ 1 day with spotting in a 35-day interval) following all four treatment intervals. The rate of amenorrhoea and the period until the appearance of amenorrhoea after each individual treatment interval, bleeding control (definition: no severe bleeding and bleeding for a maximum of 8 days during the last 56 days of a treatment interval) after each treatment interval, the fibroid volume, pain, and the quality of life were secondary effectiveness criteria. The rate of premature study dropouts on the grounds of safety (i.e., clinically significant changes in the gynaecological breast examination, ovarian ultrasound, ECG, laboratory diagnostics, vital signs, endometrial thickness, and histology, in accordance with the

Table 1: Most important results from studies PEARL I–III [11, 23, 24].

	Study design	*Study drug/- duration*	*Inclusion criteria*	*Study population*	*Primary endpoints and results*	*Secondary endpoints and results*
PEARL I [23]	*double-blind, randomized, placebo controlled, multicenter, parallel group*	*UPA 5 mg/d vs. UPA 10 mg/d vs. placebo Duration: 12 Weeks All patients received iron supplementation*	*women with uterine fibroids,hypermenorrhea (PBAC> 100), anemia (Hb < 10,2 g/dl), eligible to undergo fibroid surgery after the end of the treatment period*	*UPA 5 mg:* N = 96 *UPA 10 mg:* N = 98 *Placebo:* N = 48	*Percendays of patients with control of uterine bleeding (PBAC < 75) at week 13: UPA 5 mg: 91 %∗ UPA 10 mg: 92 %∗ Placebo: 19 % ∗P < 0,001 Reduction of fibroid volume compared to baseline (median) at week 13: UPA 5 mg: -21,2 %∗ UPA 10 mg: -12,3 %∗∗ Placebo: +3 % ∗P = 0,002 ∗∗P = 0,006*	*Percendays of patients in amenorrhea at week 13:* UPA 5 mg: 73 %∗ UPA 10 mg: 82 %∗ Placebo: 6 % ∗P < 0,001 *Menstrual bleeding:* PBAC at baseline (median) UPA 5 mg: 386 UPA 10 mg: 330 Placebo: 376 vs. at week 13: UPA 5 mg: -329∗ UPA 10 mg: -326∗ Placebo: -59 ∗P < 0,001

Table 1: Continued.

	Study design	Study drug/- duration	Inclusion criteria	Study population	Primary endpoints and results	Secondary endpoints and results
PEARL II [11]	double-blind, randomized parallel group, double-dummy, noninferiority trial	UPA 5 mg/d vs. UPA 10 mg/d vs. Leuprorelin Acetate (LA) 3,75 mg i.m. /1x Month Duration: 12 weeks	Women with uterine fibroids, Hypermenorrhea, all patients eligible for uterine fibroid surgery	UPA 5 mg: N = 93 UPA 10 mg: N = 95 LA: N = 93	Percendays of patients with controlled bleeding (PBAC < 75) at week 13: UPA 5 mg: 90 %∗ UPA 10 mg: 98 %∗∗ LA: 89 % ∗1,2 (95 % CI: -9,3 to 11,8) ∗∗8,8 (95 % CI: 0,4 to 18,3)	Percendays of patients with amenorrhea at week 13: UPA 5 mg: 75 % UPA 10 mg: 89 % LA: 80 % Median change in fibroid volume of the 3 largest fibroids at baseline and at week 13: UPA 5 mg: -36 % UPA 10 mg: -42 % LA: -53 %
PEARL III [24]	Long-term phase III UPA treatment Courses Open NETA treatment corses: double-blind, placebo controlled, randomized	Per treatment course: UPA 10 mg/d for 12 weeks followed by NETA 10 mg/d for 10 days or placebo for a total of 4 treatment courses	Women with symptomatic uterine fibroids, eligible for uterine fibroid surgery	UPA treatment Treatment course 1 N = 132 Treatment course 2 N = 131 Treatment course 3 N = 119 Treatment course 4 N = 107	Patients in amenorrhea after each treatment course Treatment course 1: 79,5 % Treatment course 2: 88,5 % Treatment course 3: 88,2 % Treatment course 4: 89,7 %	Median change in fibroid volume of the 3 largest fibroids at baseline Treatment course 1: -45 % Treatment course 2: -63 % Treatment course 3: -67 % Treatment course 4: -72 % time to amenorrhea Treatment course 1: 4 Days Treatment course 2: 2 Days Treatment course 3: 3 Days Treatment course 4: 3 Days

PBAC: pictorial blood-loss assessment chart; UPA: ulipristal acetate; LA: leuprorelin acetate; NETA: norethisterone acetate.

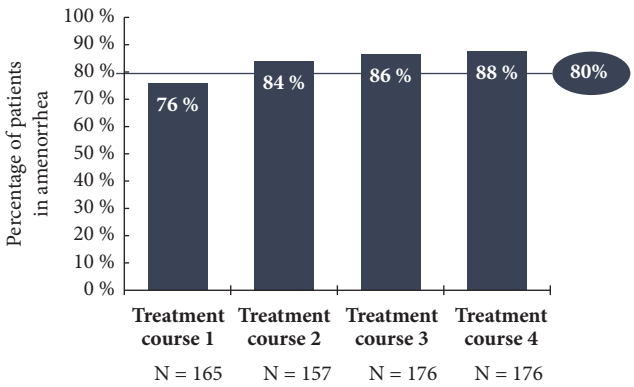


Figure 4: Percentage of patients with amenorrhoea at the end of each treatment interval with 5 mg of UPA (PP4; PEARL IV).

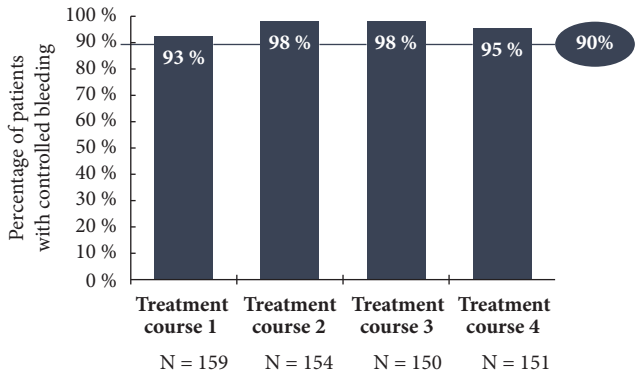


Figure 5: Percentage of patients with bleeding control at the end of each treatment interval with 5 mg of UPA (PP4; PEARL IV).

study protocol) and the frequency of side-effects were defined as endpoints for safety.

Only the results for the 5 mg UPA dose are represented in this study since only this has been approved in Germany for the treatment of fibroids. Unless otherwise stated, all data given here originate in the publication by Donnez et al., including the supplementary evaluation in the attachment (2016; Part II), and refer either to the Full Analysis Set (FAS1: all patients who were given the study medication at least once in the 1st treatment interval) or to the Per Protocol Set (PP4: all patients who were given the study medication over at least 56 days in the 4th treatment interval). In respect of the primary effectiveness criterion, an amenorrhoea rate of 48.7% was determined across all four treatment intervals. In the individual treatment intervals, the amenorrhoea rates in the Per Protocol Set (PP4) were 75.8%, 84.1%, 86.4%, and 87.5% (Figure 4). The corresponding results of the FAS1 over the individual treatment intervals were consistently high (71.8%, 74.1%, and 73.3% after intervals 1, 2, and 3) and amenorrhoea occurred in approximately 70% of the women after the 4th UPA treatment interval. The period until the occurrence of amenorrhoea in all treatment intervals was 5-6 days (median). The effects of 5 mg of UPA in respect of the bleeding control in the course of the study are represented for the Per Protocol Set (PP4) in Figure 5. In the Full Analysis Set 1, the bleeding was under control in 73.3% of the patients at the end of the 4th treatment interval; at the same time, the PBAC (pictorial bleeding assessment chart) had decreased from 224 to 77.5 (median) (Figure 6). In regard to the bleeding intensity during the treatment breaks, it was observed that a bleeding intensity PBAC of < 100 is achieved with at least two 12-week treatment intervals under UPA, which is therefore below the threshold value for hypermenorrhoea (PBAC = 100). The fibroid volume (the volume of the 3 largest fibroids was measured) decreased continually with each treatment interval in comparison with the initial value (Figure 7). The percentage of patients with a clinically significant reduction of the fibroid volume ($\geq 25\%$) increased from 62.3% after the 1st treatment interval to 78.1% after the 4th treatment interval. At 76.6% (Figure 8), this value was largely unchanged in the follow-up examination 3 months after the end of the treatment. The greatest decrease in the fibroid volume was observed after the first two treatment intervals, which shows that a second treatment interval substantially increases the therapeutic effect [9].

After the 4th treatment interval, 73.5% of all women had amenorrhoea and a decrease in the fibroid volume of $\geq 25\%$ [24]. Only 4.8% of the women treated with UPA had neither amenorrhoea nor a reduction of the fibroid volume of $\geq 25\%$ (Figure 9). Overall, 95% of the patients benefited from the long-term interval treatment with 5 mg of ulipristal acetate, so that no invasive procedure was required during the entire period of observation in over 95% of the cases.

Pain, which was recorded by means of visual analogue scale (VAS: 1 – 100), improved under the treatment and decreased from the initial score of 39 (median) after the 4th treatment interval to a value of 7 (median). The pain also remained at a low level during the treatment breaks and at the end of the follow-up and ranged between 9.0 and 22.5 [9] (Figure 10). The quality of life, which was assessed by means of the UFS QoL (Uterine Fibroid Symptom and Quality of Life) questionnaire, decreased from an initial value of 50 (median) to 15.6 after the 4th treatment interval, where this value is consistent with healthy women [9, 10]. The results of the HR QoL (Health Related Quality of Life) in the course of the study are shown in Figure 11.

The estradiol levels were in the mid-follicular range over the entire duration of the study. The Hb value showed an increase, from the initial value of 12.55 g/dl to 13.10 g/dl, after the 4th treatment interval, although, unlike the Pearl I study, anaemia was not an inclusion criterion in this study.

Undesirable reactions, which the doctor ascribed to UPA as causal, occurred in 20.4%, 13.0%, 4.7%, and 6.1% of the patients (treatment intervals 1, 2, 3, and 4). With an increasing number of treatment intervals, side-effects decreased steadily. The most frequently observed side-effects were headaches and hot flushes. After a temporary increase in the endometrial thickness in the 1st treatment interval, an endometrial thickness of > 16 mm was less and less frequently measured in the following treatment intervals [9, 10] (Figure 12). Over the entire study, according to the biopsy and histology examination, 6 cases of hyperplasia occurred. These reduced as the treatment progressed and/or during the follow-up period [9].

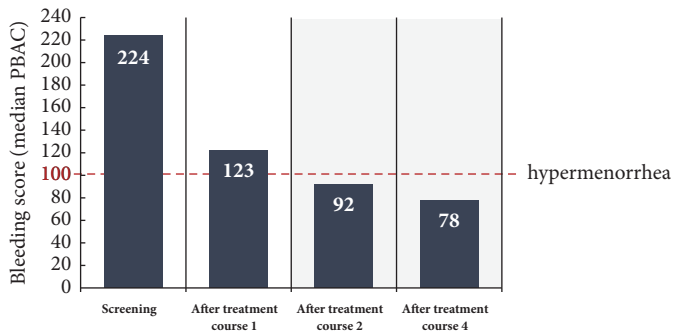


Figure 6: Bleeding intensity (PBAC median) of the first menstruation following the completion of a treatment interval (FAS1; PEARL IV).

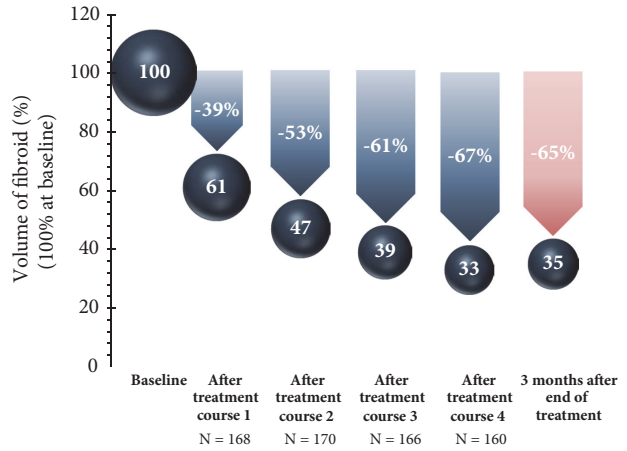


Figure 7: Volume change in the 3 largest fibroids (median) in comparison with the initial value.

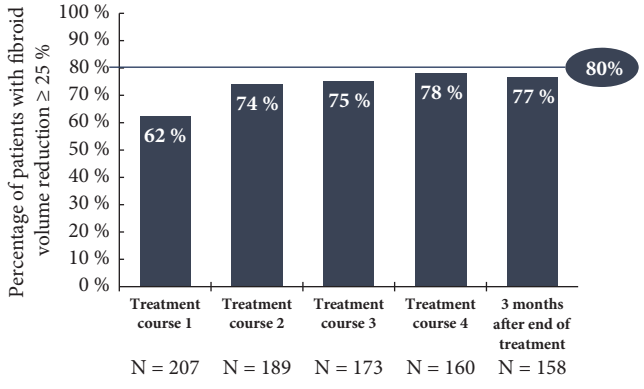


Figure 8: Percentage of patients with clinically significant reduction of the volume of the fibroids of ≥ 25% (FAS1) [9].

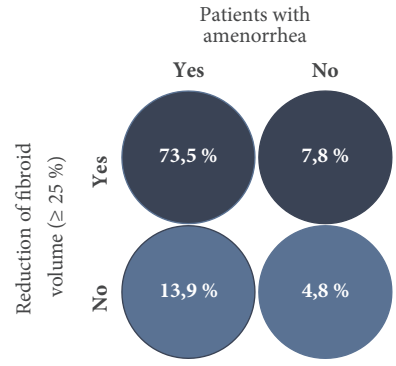


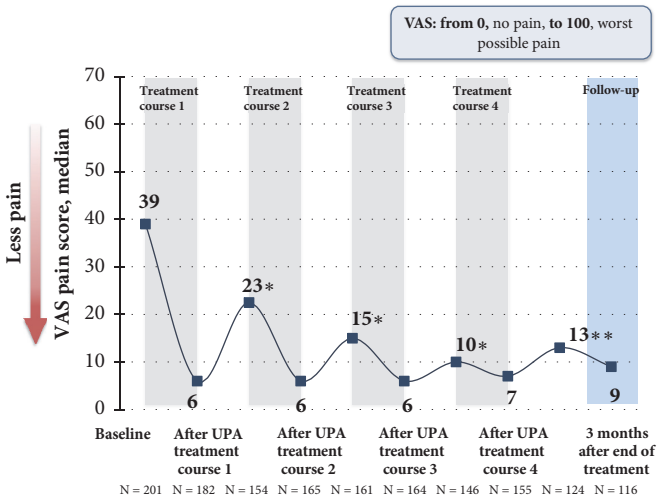
Figure 9: Percentage of patients with amenorrhoea and clinically significant reduction of the volume of the fibroids of ≥ 25% [10].

The frequency of nonphysiological endometrial changes (PAEC) at the commencement of the study was 7.8% and increased to 16.3% and 16.2% until the end of the 2nd and 4th treatment interval. In the follow-up after 3 months, nonphysiological changes of the endometrium were observed in 9% of the patients, which broadly corresponds with the initial values prior to the commencement of the study [10]. Hence, long-term intermittent treatment with 5 mg of UPA does not result in an increased incidence of PAEC (Figure 13). The further findings in the physical examination, vital signs, ECG, and sonography of the ovaries produced no reservations in regard to the safety of UPA.

The results of PEARL IV demonstrate the effectiveness and safety of UPA as an intermittent treatment for symptomatic fibroid patients, and so the approval of UPA with a daily dose of 5 mg was extended to long-term interval therapy (LIT), not limited in terms of time, in May 2015.

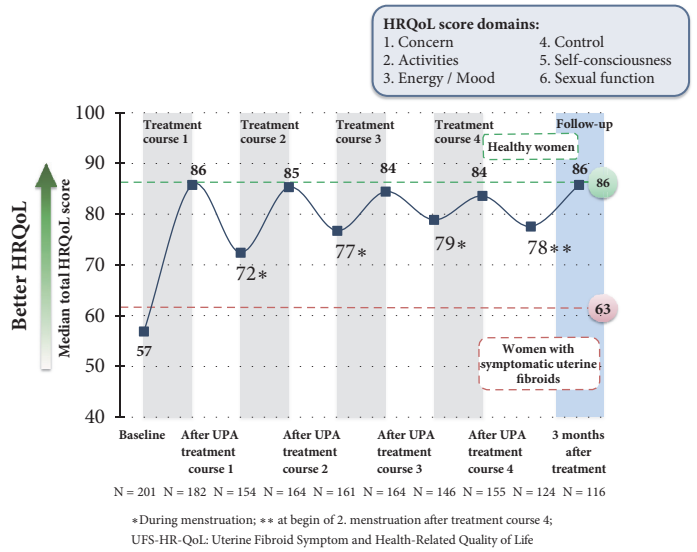
4. Significance of UPA in Clinical Practice

The application of UPA for intermittent long-term treatment for fibroids is evaluated in current publications as an asset since; for most patients, this results in rapid and reliable bleeding control, a reduction in the size of the fibroids and an improvement in the symptoms and, in many cases, can prevent a hysterectomy or fibroid enucleation [26]. Donnez et al. also share this view [9]. They describe a legitimate status for UPA in the medication-based treatment of fibroids in regard to avoiding a surgical intervention or at least as a preoperative supplementary measure.



∗During menstruation; ∗∗ at begin of 2. menstruation after treatment course 4;
VAS: visual analogue scale; UPA: ulipristal acetate

Figure 10: Effect of 5 mg of UPA on the course of pain (VAS). Outline of the median values (FAS1) [11].



∗During menstruation; ∗∗ at begin of 2. menstruation after treatment course 4;
UFS-HR-QoL: Uterine Fibroid Symptom and Health-Related Quality of Life

Figure 11: Effect of 5 mg of UPA on the quality of life (HR QoL). Outline of the median values (FAS1).

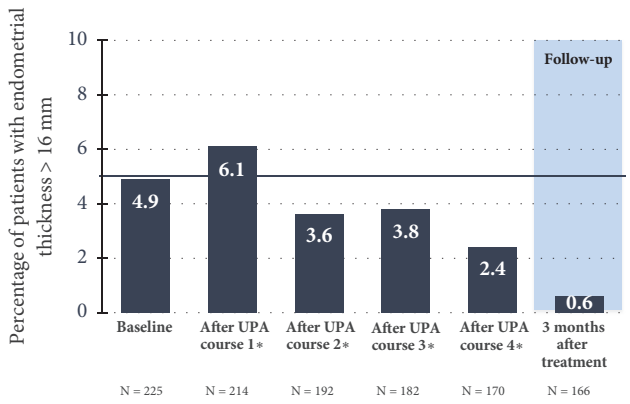
In their latest paper, Donnez and Dolmans [4] present the various possible applications of UPA in the treatment of fibroids, taking the age of the patient, the severity of the symptoms, the wish of the patient in regard to the retention of the organ and fertility, and the location and the size of the fibroids into consideration.

Type 1 Fibroids. They are < 3 cm in size: hysteroscopic myomectomy.

When the size of the fibroid is > 3 cm or with anaemia, medication-based treatment with one to two treatment intervals with UPA is conducted, each over 12 weeks. When there is a good response to the treatment, a surgical procedure may possibly be avoided.

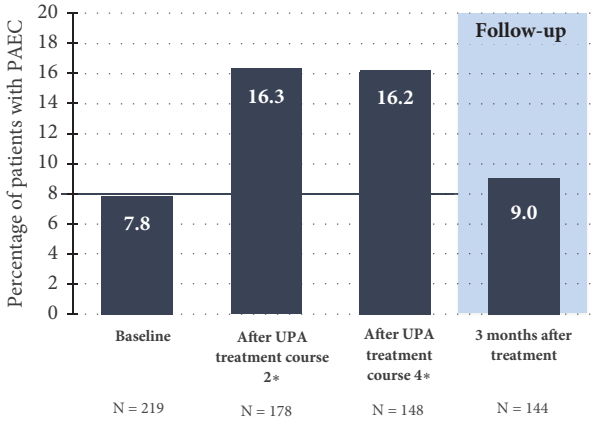
Type 2 Fibroids or Multiple Type 2-5 Fibroids. Long-term intermittent treatment with two 12-week UPA treatment intervals may be indicated for women of child-bearing age with a desire to have children. In the case of a good response (fibroid reduction of ≥ 25 – 50%, no deformation of the uterine cavity) or very good (fibroid reduction of > 50%, no deformation of the uterine cavity) response to the treatment, the possibility of a normal conception is a given. When there is an inadequate fibroid volume and/or bleeding response and when there is existing deformation of the uterine cavity, a hysteroscopic myomectomy may be necessary.

For women of child-bearing age who do not wish to have children or for premenopausal women who wish to retain the organ, long-term intermittent treatment with four 12-week



∗Assessment after UPA treatment course + 1 menstrual cycle
UPA: Ulipristal acetate

Figure 12: Percentage of patients with an endometrial thickness of > 16 mm (Safety Population) [10].



∗Assessment after UPA treatment course + 1 menstrual cycle; UPA: Ulipristal acetate

Figure 13: Percentage of patients with nonphysiological changes of the endometrium (PAEC) (Safety Population).

UPA treatment intervals can be recommended. When there is a good response (volume reduction of ≥ 25%, bleeding control), the treatment can be suspended until the recurrence of symptoms; otherwise, a surgical procedure is indicated. For women of child-bearing age, a fibroidectomy can be performed when there is an inadequate response to the medication-based treatment. A UAE is also a possibility for premenopausal women who wish to retain the organ.

5. Conclusion

UPA is suitable for the treatment of fibroids, both for preoperative use and for intermittent long-term treatment. It has been shown in clinical studies that bleeding is successfully controlled by the administration of 5 mg per day, over 12-week treatment intervals each time. For most women, amenorrhoea starts within a few days and anaemia is corrected. UPA also causes a reduction in the size of the fibroids, an improvement in the pain, and, overall, results in a distinct improvement in the quality of life of the affected patients. In terms of bleeding control and fibroid reduction, the effects are increased without an increased rate of side-effects or the occurrence of endometrial changes by the initial administration of a least two UPA treatment cycles. Clinical practice experience shows that, after a twofold treatment (each of three months) in particular, the interval before a required third treatment can often be extended further (between 6 and 12 months) [27].

Despite the PRAC's new measures to minimize the risk of rare but serious liver injury the use of the SPRM ulipristal acetate still presents new therapeutic perspectives, particularly for symptomatic fibroid patients for whom the wish to retain the organ or fertility is a priority.

Disclosure

This article is a translated version of the original article entitled "Anwendung von selektiven Progesteron-Rezeptor-Modulatoren (SPRMs) zur medikamentösen Behandlung von Uterusmyomen: Ulipristalacetat im Fokus" authored by Rabe, T. et al., which has been published in *J. für Reproduktionsmedizin und Endokrinol.* **14,** 113–122 (2017). Permission has been granted by the authors and the original publisher Krause und Pachernegg GmbH. The translated version of the manuscript has been updated to provide information on the current recommendations by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) to minimize risk of rare but serious liver injury.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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Review Article

Prevention and Management of Complications in Laparoscopic Myomectomy

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Myomectomy aims to preserve fertility, treat abnormal uterine bleeding, and alleviate pain. It should cause minimal damage to the endometrium, while being tolerable and durable, and reduce the incidence of myoma recurrence and complications including bleeding, hematoma, adhesions, and gravid uterus perforation. Training and experience are crucial to reduce complications. The surgical strategy depends on imaging information on the myomas. The position of the optical and secondary ports will determine the degree of ergonomic surgery performance, time and difficulty of myoma enucleation, and the suturing quality. Appropriate hysterotomy length relative to myoma size can decrease bleeding, coagulation, and suturing times. Bipolar coagulation of large vessels, while avoiding carbonization and myometrium gaps after suturing, may decrease the risk of myometrial hematoma. Quality surgery and the use of antiadhesive barriers may reduce the risk of postoperative adhesions. Slow rotation of the beveled morcellator and good control of the bag could reduce de novo myoma and endometriosis. Low intra-abdominal CO_2 pressure may reduce the risk of benign and malignant cell dissemination. The benefits a patient gains from laparoscopic myomectomy are greater than the complication risks of laparoscopic morcellation. Recent publications on laparoscopic myomectomies demonstrate reduced hospitalization stays, postoperative pain, blood loss, and recovery compared to open surgery.

1. Introduction

Uterine fibroids are a common disorder with an estimated incidence of 20–40% in women during their reproductive years [1, 2]. Myoma diagnosis has been substantially improved in the last decade, mainly due to higher sensitivity and specificity of imaging modalities and improved knowledge about how a myoma alters normal endometrial function. The frequency of myoma varies according to age, inheritance, and possibly body mass index [3]. The fact that more women are seeking childbirth at a later age increases the frequency of infertility due to myoma presence, and reduces the implantation potential. Submucous and intracavitary myomas are usually operated on using hysteroscopy, while subserous myomas are approached with laparoscopy. In comparison, intramural myomas can be operated by hysteroscopy or laparoscopy depending on the size (<4 cm) and surgeon's experience. The number, size, location, and vascularization of a myoma as well as the experience of the surgeon predict the outcome of the operation and subsequent risk of complications [3].

Recent studies demonstrate that the complications after myomectomy have been increasing in the last decade [4, 5]. This trend can partially be attributed to the shift toward

childbearing at a later age. Problems with infertility, as well as progressively larger myomas that are also increasing in number, are more common in this age group. A growing number of gynecologists with unjustified confidence at myoma excision by minimally invasive surgery (MIS) without sufficient training in laparoscopic suturing and electromechanical morcellation might also be attributed to these statistics [6]. In 2002 a meta-analysis reported a similar number of intra- and postoperative complications after gynecological operation performed by laparotomy or by laparoscopy [7]. Another meta-analysis on 6 RCTs with 576 patients comparing laparoscopic versus open myomectomy, demonstrated that laparoscopic myomectomy was associated with faster postoperative recovery by day 15, reduced operative blood loss, diminished postoperative pain, and fewer overall complications. Authors concluded that laparoscopic myomectomy, performed by a specialized surgeon and with more stringently selected patients, is a better choice than open surgery [8].

Injuries may be direct, such as by organ damage due to morcellation. Alternatively, an indirect injury could occur while performing MIS on a sarcomatous tissue of a presumed myoma. This would result in the spreading of malignant cells, causing peritoneal parasitic myoma or endometriosis. Complications might arise due to incorrect selection of the patients, failure to limit time in laparoconversion, and surgeons' overconfidence in managing difficult cases [9, 10]. The intraoperative and postoperative laparoscopic myomectomy complications as well as preventive measures are reviewed below.

2. Methods

A systematic review on published studies in PubMed, EMBASE, CBMdisc, Ovid, and Cochrane, with cross-referencing, was performed. Myomectomy after laparoscopy, hysteroscopy, and complications were the main key words used to isolate the relevant articles.

2.1. General Considerations. Laparoscopic myomectomy complications can be intraoperative due to inappropriate hysterotomy, enucleation, hemostasis, and morcellation injuries. Alternatively, the complications may be postoperative due to hysterotomy site hematoma and adhesions, pelvic adhesions, and recurrence. Obstetric complications after laparoscopic myomectomy are also possible. Laparoscopic resection of 654 fibroids, with a mean myoma size of 5.3 cm, had an intraoperative complication rate of 2.6% and postoperative complications occurred in 5.7% of patients [4]. In another study, of 2,050 laparoscopic myomectomies, the total complication rate was 11.1% (225/2050 cases) [11].

In another study, laparoscopic myomectomy was performed in 505 women, removing 912 myomas, and 184 (36.4%) patients had multiple myomectomies. A comparison between the size of the myomas (<10 cm and ≥10 cm in largest diameter) and number of myomas removed (≤4 and ≥5 myomas) was performed. The mean blood loss, duration of surgery, and hospital stay were greater in the groups with multiple and larger myomas [12]. An odds ratio was computed to estimate the risk of complications in relation to the patient characteristics which showed that the probability of complications significantly rises with an increase in number of myomas (more than 3 myomas OR: 4.46, $p < .001$) and with either intramural (OR: 1.48, $p < .05$) or intraligamentous location of myomas (OR: 2.36, $p < .01$), whereas the myoma size seems to primarily influence the risk of major complications (OR: 6.88, $p < .001$) [13].

Authors in the above studies concluded that laparoscopic myomectomy, when performed by an experienced surgeon, can be considered a safe technique with an extremely low failure rate, low complication rate, and good results in terms of subsequent pregnancy outcomes [11–13]. Table 1 demonstrates that the risk of longer operation time, blood loss, blood transfusion, and hysterectomy hematoma is higher with increasing size of the myoma. Furthermore, a double-blind study on pain control comparing 19 cases after laparoscopic myomectomy and 21 after laparotomy showed that laparoscopic surgery had clear advantages over laparotomy as far as pain control is concerned [13].

2.2. Intraoperative Complications. Excessive blood loss, myometrial hematoma, and morcellation accidents are the most frequent intraoperative complications during laparoscopic myomectomy. The risk factors contributing to intraoperative bleeding are insufficient use of vasoconstrictive agents, fibroid size, fibroid position, number of fibroids, failure to identify the cleavage plane, failure to identify the feeding vessel, insufficient hemostasis, lack of precision in suturing, loose knotting, and surgeon inexperience (Table 3) [10]. Uterine wound approximation problems present as the most frequent intraoperative complications when adenomyosis/adenomyoma is present.

In hysterotomy, the incision is performed along the trocar projection line and is used for the needle holder and direction of suturing. The incision length depends on the fibroid size, how much it bulges, and its orientation. The size of the incision should be similar to the length of the myoma. The selection of the incision area, orientation, and length will determine the degree of difficulty of myoma enucleation, suturing, and amount of bleeding. The reported usual volume of bleeding ranges from 84 to 1200 mL according to several papers [15–18]. The excessive bleeding and failure to control it are also the major reasons for conversion to laparotomy, which has been reported between 0.34% and 2.7% [9, 11, 18, 19]. These authors agree that, increasing the number and size of the fibroids, the hemorrhage risk of bleeding is increasing. Complications due to incomplete myoma excision create the possibility of continuous bleeding over several weeks, intermittent bleeding to menometrorrhagia, single pain episodes, severely painful dysuria, chronic cystitis, constipation, and bowel spasms. Very seldom peritonitis occurs, and there is a higher recurrence rate in these cases [10].

Very large myomas have fewer reports. Laparoscopic Excision has been reported in 51 women with at least one myoma larger than 9 cm. Overall 78 myomas were operated with a mean operating time of 136.67 ± 38.28 minutes (range 80–270 min) and mean blood loss 322.16 ± 328.2 mL (range 100–2000 mL). One patient developed a broad ligament hematoma, two developed postoperative fever, and

Table 1: Comparison of hysterotomy scar hematoma after laparoscopic myomectomy.

Study	Patients	Myoma number	Myoma mean size cm	Operation average time min	Blood loss	Blood transfusion	US Hysterotomy scar hematoma
Sinha et al., 2003 [14]	51	78	>9	137	323 ml	1 (1.3%)	1 (1.3%)
Altgassen et al., 2006 [4]	351	654	5.3	113	ND	1	(29.2%)
Sizzi et al., 2007 [11]	2050	ND	6.4	ND	14 (0.68%) hemorrhage	3 (0.14%)	10 (0.48%)
Sinha et al., 2008 [12]	505	912	5.9	60	90 ml	ND	ND
Mettler et al., 2012 [10]	335	480	4–9	90	157 ml	0	21 (6.2%)

Note. ND: no data.

one underwent open subtotal hysterectomy 9 hours after surgery for dilutional coagulopathy. Authors concluded that myomectomy for very large fibroids by laparoscopy is a safe alternative to laparotomy for very large myomas [20].

2.3. Postoperative and Long-Term Myomectomy Complications. Intra-abdominal and intrauterine adhesions are delayed postmyomectomy complications. The use of antiadhesive agents might be helpful for reducing postoperative adhesions; however, strong evidence for this in the literature is missing [10]. A prospective observational study, performing hysteroscopy in 51 infertile patients three months after myomectomy, reported intrauterine adhesions (IUA) in 11 out of 51 (21.57%) cases. No significant relationship was found between IUA and the type, size, or number of fibroids. Additionally, no relationship was found between use of IUA and endometrial trauma during the myomectomy. Postoperative hysteroscopy is highly recommended to diagnose and treat these adhesions early [20].

When concomitant pathologies exist such as focal adenomyosis and adenomyoma, or in large intramural and submucous myoma extractions, myometrium approximation becomes a big challenge. Sometimes a gap left between the wound edges cannot be avoided. Accordingly, a postoperative follow-up is recommended and a comment in patient's discharge report is advisable. Special attention should be paid to these patients, especially if the decision is made to pursue spontaneous delivery.

Obstetric complications due to uterine perforation during labor are caused mainly due to weak myometrium after destruction by extensive coagulation and/or myometrial tissue injury, or after defective suturing and poor tissue approximation. Preoperative assessment of submucosal fibroids is essential for the decision on the best approach for treatment. In the infertile population, cumulative pregnancy rates by the laparoscopic and the minilaparotomy approaches are similar, but the laparoscopic approach is associated with a quicker recovery, less postoperative pain, and less febrile morbidity [3].

Evaluating the obstetric complications, the pregnancy rate in term infants was 57.1% after myomectomy without any uterine rupture as reported by Altgassen et al. [4]. Among patients wanting pregnancy after myomectomy, the pregnancy rate of 69.8% was noted and only one (0.26%) recorded a spontaneous uterine rupture at 33 weeks' gestation [21]. In another series of 1,032 laparoscopic myomectomies there were only 6 obstetric complications [10]. Out of 130 patients desiring pregnancies, 78 (60%) became pregnant. Among the 78 pregnancies, there were 6 abortions, 60 spontaneous deliveries, and 18 caesarean sections. Eight sets of twins and one set of triplets were reported [10]. The reported uterine rupture rate in 3rd trimester pregnancies and women in labor is quite small and the major reason leading to this complication is myometrium insufficient healing [22].

2.4. Morcellation Complications. The exact incidence of morcellation complications is unknown and likely underestimated. Medical literature mainly describes case reports and the vast majority of complications after tissue power morcellation are not reported.

2.4.1. Direct Injury. A systematic review of surgical centers performed in the United States from 1993 to 2013 registered 55 morcellator-related complications. Organs injured included large bowel ($n = 31$), vascular system ($n = 27$), the kidneys ($n = 3$), ureters ($n = 3$), the bladder ($n = 1$), and the diaphragm ($n = 1$). Significantly, in six cases, it was reported that patient death followed. The complications were noted intraoperatively in most patients (66%); however in the remainder of cases they were not identified for up to 10 days after operation. This finding was attributed to surgeon inexperience [5]. It has been reported that the overall probability of direct power morcellator injuries to internal organs is more frequent (0.12%) than morcellator injuries to the abdominal and pelvic wall (0.06%). A survey of ESGE physicians found that most had not experienced bladder, ureter, or aorta and vessel injuries during morcellation. However, three surgeons with morcellator experience did report causing permanent damage. In contrast to the findings of M. P. Milad and E. A. Milad, no death was reported. Morcellator technical problems were also found to be a rare issue (0.12–0.3%), with transient stacking being the most frequent issue. Ultimately, direct morcellator injury is a reportedly rare occurrence. Despite the low risks, the ESGE board maintains that only

Table 2: De novo myoma and endometriosis formation after laparoscopic myomectomy/hysterectomy.

Study	Type of study	Study details	Parasitic myoma%	Parasitic endometriosis%
Tanos et al., 2016 [23]	EGSE Survey	191 doctors participated	0.08	0.16
Meulen et al., 2016 [24]	Meta-analysis 44 studies	Laparoscopic morcellation and myomectomy	0.12–0.95 0.2–1.2	ND
Schuster et al., 2012 [25]	Case control	277 LASH morcellations, 187 VH or TAH	ND	1.4 1.4
Donnez et al., 2007 [26]	Retrospective	8 out of 1405 LASH cases	ND	0.65

Note. ND: no data, LASH: laparoscopically assisted subtotal hysterectomy, VH: vaginal hysterectomy, and TAH: total abdominal hysterectomy.

Table 3: Intraoperative bleeding during laparoscopic myomectomy without any vasoconstrive measures.

Study	Myoma type	Patients number	Myoma size cm	Myoma multiple	Bleeding ml	Hospitalization	Conversion to LMY
Sizzi et al., 2007 [11]	ND	2050	>4	48	ND	ND	0.34
Tinelli et al., 2012 [15]	SS + IM	235	4–10	48	118 +/− 28	86% 48 hs	0
Malzoni et al., 2006 [30]	IM -75%	982	6.7 +/− 2.7	47	3/982	ND	1.29
Sankaran and Odejinmi, 2013 [31]	ND	125	7.6	3.7	ND	ND	1.6
Dubuisson et al., 1995 [32]	IM	71	>5	ND	ND	ND	2.7
Saccardi et al., 2014 [33]	ND	444	8–12	ND	2/444	ND	1.35
Walid and Heaton, 2011 [16]	ND	41	2–15.6	ND	2–1200 ml	ND	ND
Mallick and Odejinmi, 2017 [19]	IM 49% SS 33%	323	7.7 +/− 2.8	4 +/− 3.6	279 +/− 221	1.9 +/− 0.95 days	0.62
diZerega, 1997 [18]	IM 34% SS 19%	54	>3	ND	84	2.09 days	1.8
Mathew et al., 2013 [34]	ND	1,001	ND	44	248 mL avg, 1 transf	1–5	1 death pop unexp

Note. ND: no data.

physicians with adequate training and knowledge should be performing these endoscopic procedures in order to avoid these rare, but serious complications [27].

2.4.2. Indirect Injury. The overall incidence of parasitic fibroids after laparoscopic surgery in general with the use of morcellation was reported to be between 0.9% and 0.12% [24, 28, 29]. The reported incidence of parasitic myomas after laparoscopic myomectomy was found to be 0.2–1.2% [28, 29] (Table 2). In a survey study the risk for parasitic myoma after myomectomy was reported as 0.08% [24], much lower than 0.12–0.95% found after a meta-analysis of 44 studies [28].

Posthysterectomy pelvic adenomyotic masses were observed in 8 out of 1,405 (0.65%) after laparoscopic subtotal hysterectomies [35]. In a case control study after 277 laparoscopic supracervical hysterectomy (LASH) with uterine morcellation compared with 187 patients after VH or TAH (no morcellation), the de novo diagnosed endometriosis was 1.4% (3/217) in the LASH group and 1.4% (2/145) in the control subjects. The risk of de novo formation of endometriosis after adenomyoma morcellation is much higher 0.16% and may be attributed to the fact that many endometriosis cells are already buried below the peritoneal epithelium while immunological factors might also be involved in favor of dissemination and growth [24]. In addition, 25% of the enlarged uteri with myomas might also concomitantly include adenomyosis [23, 26].

The risk of parasitic myoma and de novo endometriosis after laparoscopic myomectomy might be also explained by the fact that this operation is performed more often in premenopausal women with higher estrogen levels [23, 35]. Postmenopausal women treated with HRT have a higher risk of de novo tissue complication; hence patients should be informed accordingly prior to the operation. The time of exposure to morcellation process, larger tissue volume to be morcellated, greater amounts of fragments released, and the higher CO_2 intra-abdominal pressure needed may all contribute to rising the risk of de novo formation of uterine tissue implantation. Stabilization of the specimen prevents fast rotation and spread of cells and tissue fragments in

the abdominal cavity while in-bag morcellation is another option, although it is still under investigation. Efforts should be made to remove all tissue fragments after morcellation and use thorough irrigation and suction in the peritoneal cavity.

The survival rate of patients with leiomyosarcoma operated on by laparoscopy with myoma morcellation has been reported to be decreased, concluding that primary surgery involving tumor injury seems to be associated with a worse prognosis [36–38]. The benefits of myomectomy should be weighed against the risks, and management of fibroids in perimenopausal women should be individualized. Whether power morcellation poses a unique danger to the patient with occult LMS is still an unanswered question [38]. Patients over the age of 40 with myomas >8 cm in diameter, with hypervascularity and necrosis recorded in ultrasound and MRI are considered highly suspicious for leiomyosarcoma [37]. Rossetti et al., in their review published in April 2001, looked at the rate of myoma recurrence following either laparoscopic or laparotomic myomectomy (162 patients, 82 for each type of surgery) [39]. Patient follow-up continued for up to 40 months. At the end of this time, 11 in the laparoscopy and 9 in the laparotomy group had suffered a recurrence. Analysis did not show any statistical significance [39]. The higher the number of fibroids and the larger the size of the myoma, the higher the risk of recurrence [40].

2.4.3. Prevention of Late Complications of Morcellation. To minimize the risk of upstaging uterine sarcomas and benign tissues such as fibroid and endometriosis tissue, power morcellation of a presumed fibroid can be performed in a laparoscopic bag. Research in tissue retrieval from the abdominal cavity mainly focuses on in-bag tumor morcellation. Evidence suggests that in-bag tumor morcellation may prevent parasitic fibroids, reduce the risk of upstaging premalignant lesions, and offer protection from direct morcellation trauma [41–43]. In urology, in-bag morcellation after laparoscopic removal of early stage and low-grade renal cell carcinoma is reported to be safe and effective. Of course, in aggressive manipulations or especially in difficult cases the laparoscopic bags can be torn. In these instances, spillage of tumor cells can occur. The use of methylene blue dye in the lap-bag has been suggested in order to create awareness once spillage has occurred. Transvaginal in-bag morcellation has also been described; however further prospective and well-designed studies are needed before establishing the potential value of in-bag morcellation in gynecologic surgery [21, 42–44].

2.5. Strategies to Prevent Possible Surgical Complications

2.5.1. Imaging and Evaluation of Fibroids for Malignant Changes. The anatomic location and the features of a myoma are important parameters for planning the operation. The surgery outcome and the risk of intraoperative complications are highly dependent on trocar placement, finding of the correct cleavage plane, hemostasis, and suturing technique. Preoperative differentiation between myoma, adenomyoma, and LMS of vital importance will define the way of surgery. Ultrasonographic diagnosis is the primary and most effective screening tool to investigate fibroid size, number, and location with high precision [45]. For cases that need further investigation regarding the fibroids proximity to adjacent organs, or that are suspicious of being a sarcoma, MRI is recommended to follow. The MRI can provide more details, such as information about increased vascularity and necrosis. Where multiple fibroids with complex morphology are found, the surgeon should be highly suspicious of a sarcoma [46]. The reproducibility of MRI is higher than US regarding the very big size and number of fibroids.

Occasionally high contrast sonography and/or hysteroscopy can evaluate the uterine cavity involvement and surgeon might suggest GnRHa prior to surgery. This is important for infertility treatments, where conservative myomectomy is crucial in determining future embryo implantation and term pregnancy potential. The diagnosis of a big intramural myoma, involving also the junctional zone of the endometrium, is crucial to be noted by the surgeon prior to the operation. Also methylene blue dye can be injected intracavitary, to easily recognize the entry into the endometrial cavity during surgery [47]. The development of new technologies in diagnostic procedures like 4D and hysterocontrast-sonography, MRI, and ambulatory hysteroscopy has assisted in early diagnosis and accurate follow-up.

There are no imaging techniques that can demonstrate any characteristic features for leiomyosarcoma (LMS) [48–50]. Ultrasound comparison between eight LMS and three STUMPs with 225 fibroids demonstrated that LMS were significantly larger, solid tumors with diameter ≥8 cm, than other uterine smooth muscle tumors [51]. However, rapid increase in size (within 3 months) is generally not distinctive as it may occur in benign fibroids as well [52–54]. High central vascularity, combined with other sonographic findings, increases the positive predictive value to 60%, but sensitivity decreases to 75%. Detecting sarcomas by 2D US and Power Doppler (USPD) findings mainly depends on the nature of the tumor. The peak systolic velocity sensitivity is about 80% and the specificity 97%. No studies on sarcoma diagnosis have been published on vascular indices measured by 3D USPD. Degenerative cystic changes can be also observed as well with an increased peripheral and central vascularity. LMS have a similar appearance to fibroids on US and MRI [49, 52]. However, a large >8 cm, solitary, oval shaped, highly vascularized and irregular, heterogeneous myometrial tumor with central necrosis/degenerative cystic changes and absence of calcifications should raise suspicion of a LMS [48, 51, 55, 56].

2.6. Preventive Measures

2.6.1. Medical Management Facilitating Laparoscopic Myomectomy, Reduction of Myoma Size. Systemic hormone therapy and contraceptives are generally the first line of treatment, especially for patients with heavy menstrual bleeding. Nonhormonal treatment options are also available, such as tranexamic acid and nonsteroidal anti-inflammatory agents [57]. Another option is the use of Gonadotropin-releasing hormone (GnRH) or ulipristal acetate as a preoperative measure for large myomas in order to reduce the risk of hemorrhage [58–60]. Usually with treatment for 6–8 weeks,

fibroids shrink by 30–50%. The use of these agents should not exceed the 6–8 weeks, as they can obscure the tissue planes between fibroids and the myometrium, making enucleation difficult and increasing the chance of myoma recurrence [61]. Once this agent is discontinued, myoma regrowth occurs; hence the timing of the operation close to the end of the treatment is necessary. Both the cost of the medication and the risk of cleavage plane lost must be weighed against the benefits when deciding whether or not to use them.

2.6.2. Management of Anemic Patients. Resolution of preoperative anemia can be achieved by a number of ways, including intravenous or oral administration of iron supplement and folic acid, administration of oral contraceptive pills, or administration of another hormonal medication used to stop or decrease severe menstrual bleeding. As previously mentioned GnRHa treatment can be used preoperatively to reduce myoma size and vascularization and thereby prevent hemorrhage. Drugs that modulate progesterone action, such as ulipristal acetate, may also decrease symptoms and shrink fibroids. Ulipristal acetate is approved for three months of therapy prior to myomectomy. Treatment with ulipristal acetate also can achieve substantial volume reduction and cease metrorrhagia [62, 63].

A systematic review and meta-analysis of randomized controlled trials on GnRHa administration prior to laparoscopic myomectomy reported 3 studies with 168 patients. Pretreatment with GnRHa did not reduce operative time, but a significant reduction of the intraoperative blood loss was noted. 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. None of the patients in the studies experienced any major intraoperative or postoperative complications, and only 1 patient in each group required blood transfusion [64].

2.6.3. Prevention of Adhesion Formation. The risk of adhesion formation on hysterotomy site and pelvis after laparoscopic myomectomy has been reported up to 92% and 76%, respectively [65–67]. Use of antiadhesive barriers may reduce the risk of postoperative adhesion formation. However, good surgery with respect to minimal destruction and handling of the healthy tissue, avoiding unnecessary organ manipulation, controlled bleeding, minimal coagulation, and reasonable operating time remain the best ways to diminish the risk of adhesion formation [68]. Physical barriers, oxidized regenerated cellulose, icodextrin, and other materials are all used to cover the myomectomy wound as a preventive measure against adhesion formation [69]. There is no conclusive evidence on the relative effectiveness of these interventions. Low quality evidence suggests that oxidized regenerated cellulose (Interceed), expanded polytetrafluoroethylene (Gore-Tex), and sodium hyaluronate with carboxymethylcellulose (Seprafilm) may all be more effective than no treatment in reducing the incidence of adhesion formation following pelvic surgery including myomectomy [70].

3. Discussion

Control of bleeding is of paramount importance after myoma enucleation. Bipolar diathermy is preferable to monopolar diathermy, as it targets only the big vessels and causes less destruction to healthy myometrium. Hemostasis should be avoided for micro bleeders in order to facilitate healing process. Excessive coagulation and carbonization should be avoided since it can be detrimental to myometrial healing. Using bipolar diathermy, a dissecting grasper, and a suction cannula, meticulous exploration of the dissection field can more efficiently detect and coagulate any actively bleeding vessels. Injection of ADH (vasopressin derivative solutions) or diluted adrenalin around the fibroid wall (extracapsular) causes blood vessels to constrict and minimizes the bleeding to facilitate dissection. Similarly, temporary bilateral uterine artery clipping can reduce blood supply and bleeding during myoma excision [71]. Additionally, the use of preoperative treatment to improve the hemoglobin concentration and diminish myoma size primarily applies to infertility cases where the myomas deform the cornua and the endometrial cavity.

Appropriate use of imaging and planning is of high importance. These tasks will help with the positioning of the optical and secondary ports, which greatly define the degree of ergonomic surgery performance, the amount of time required, and the difficulty of myoma enucleation and suturing. The use of antiadhesive barriers may reduce the risk of postoperative adhesion formation as well. However, good surgery with respect to minimal destruction and handling of the healthy tissue, avoiding unnecessary organ manipulation, controlled bleeding, minimal coagulation, and reasonable operating time remain the best ways to diminish the risk of adhesion formation [68].

Parasitic myomas are a known risk of laparoscopic myomectomies. Although they occur rarely, in up to 0.9% of cases, they should be avoided. Ongoing research suggests that morcellation in open bag, with slow blade rotation and controlled by beveled longer tip placed anteriorly, can probably reduce cell dissemination of parasitic myoma and endometriosis. Additionally, appropriate intra-abdominal CO_2 pressure may also reduce the risk of cell dissemination [41].

Even with the use of in-bag morcellation, these devices should not be applied to remove suspected malignant tissues. Low-risk patients should be adequately informed preoperatively that morcellation can spread cancer cells in the unlikely case of hidden malignancy and not be falsely assured that uterine masses are not cancerous. An objective explanation that there is no way to completely exclude cancerous cells within the myometrium or in a myoma should be offered [36, 37].

Training and experience are crucial in reduction of laparoscopic myomectomy complications. Knowledge about assembly and use of the morcellator can help to avoid device technical accidents and direct injuries. Direct visualization by placing the device, maintenance of pneumoperitoneum, careful placement of the morcellation blade as previously described, and handing the to the morcellation tenaculum

rather than moving the tenaculum to the specimen can all minimize power morcellation accidents.

The patient's safety in laparoscopy depends upon patient selection, surgeon's training and skills, equipment fidelity, instrument reliability, and hospital directives and policies. The patient selection depends directly on surgeon's capabilities and indirectly on hospital directives. Recent evidence based studies have shown that certain exercises and training can improve both novices' and experts' skills far more than the traditional apprentice–student method [72]. The patients' safety after laparoscopic myomectomy is preserved, presenting excellent treatment results with short hospitalization stays, immediate mobilization, and reduced postoperative pain.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Modern Myoma Treatment in the Last 20 Years: A Review of the Literature

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Myomas, also known as fibroids, are a specific characteristic of the human species. No other primates develop fibroids. At a cellular level, myomas are benign hyperplastic lesions of uterine smooth muscle cells. There are interesting theoretical concepts that link the development of myomas in humans with the highly specific process of childbirth from an upright position and the resulting need for greatly increased "expulsive" forces during labor. Myomas might be the price our species pays for our bipedal and highly intelligent existence. Myomas affect, with some variability, all ethnic groups and approximately 50% of all women during their lifetime. While some remain asymptomatic, myomas can cause significant and sometimes life-threatening uterine bleeding, pain, infertility, and, in extreme cases, ureteral obstruction and death. Traditionally, over 50% of all hysterectomies were performed for fibroids, leading to a significant healthcare burden. In this article, we review the developments of the past 20 years with regard to multiple new treatment strategies that have evolved during this time.

1. Introduction

Myomas or fibroids are the most common benign tumor of the female reproductive system, and while many remain asymptomatic, their impact on individual well-being can be significant [1, 2]. Traditionally, myomas have been the leading cause for hysterectomy, making this surgery the third most common surgical intervention worldwide [3, 4]. Removal of the uterus, while offering a definitive solution to the problem of fibroids, is inacceptable to women desirous of (further) childbearing or to some women simply because of psychological reasons. As a result, surgical myomectomy has been an alternative treatment option for over 100 years, originally by laparotomy and lately through minimal invasive techniques such as laparoscopy or hysteroscopy [5].

Any surgical intervention carries a small but real risk for complications: bleeding, possible need for transfusion, associated HIV and/or HCV-Infection, injury to bladder, bowel or ureters, subsequent adhesion-formation, complications of anesthesia and of hospitalization in general. Also, surgery requires a considerable infrastructure, including anesthesia, and remains cost-intensive.

Because of this, over the years conservative approaches that avoid surgery have been introduced, tested, reviewed, partially discarded, and partially accepted, leading to the currently available treatment options, as summarized in Table 1.

In this review we give updated information on the most recent literature to provide state of the art counseling to patients desirous for a thorough discussion of all available treatment options.

As increasing age during reproductive years, decreasing number of pregnancies, and increasing age of first pregnancy all lead to an absolute increase in myoma incidence, while increasing the number of women for whom hysterectomy is not an option; discussions about uterus-conserving interventions have been gaining momentum over the past 20 years [6].

This has subsequently lead to an increase in available uterine conserving treatment options.

Table 1: Treatment options for uterine myomas.

(1)	Oral contraceptive pills (symptomatic control of pain/bleeding)
(2)	Levonorgestrel-intrauterine device (IUD) (symptomatic control of pain/bleeding)
(3)	Ulipristal acetate treatment
(4)	Myoma embolisation by interventional radiology (induced ischemic myoma necrosis and shrinkage)
(5)	High frequency ultrasound treatment (induced thermic myoma necrosis and shrinkage)
(6)	Hysteroscopic myomectomy
(7)	Laparoscopic/open myomectomy and uterine reconstruction
(8)	Laparoscopic/open/vaginal hysterectomy

Table 2: Pubmed yield of different disease-specific keywords.

Fibroids	22332
Uterine fibroids	22052
Myoma	5408
Uterine myoma	22051
Leiomyoma	21001
Uterine leiomyoma	21001
Benign uterine tumors	5735

Table 3: Pubmed yield of different procedure specific keywords.

Myoma treatment	2611
Myoma treatment randomized trial	137
Conservative myoma treatment	121
Hormonal myoma treatment	126
Surgical myoma treatment	1599
Fibroid treatment	11555
Fibroid treatment randomized trial	487
Conservative fibroid treatment	333
Hormonal fibroid treatment	510
Surgical fibroid treatment	6724

2. Materials and Methods

A literature search was performed using Medline as the main resource. First, diagnosis-related keywords such as "myoma," "fibroids," "leiomyoma," and "benign uterine tumors" were initially used, yielding between 5000 and 22000 hits (Tables 2 and 3). By comparison, "breast cancer" results in 337149 hits.

The first documented, and still available, article was published in 1887 by Dr. Thomas Keith in the British Medical Journal: "Results of Supravaginal Hysterectomy, with Remarks on the Old Way and the New of Treating Uterine Fibroids" [7]. It is a fascinating article and can only be recommended as a humbling experience with regard to how slow medical progress can truly be. Also, in the second sentence of the article, a mortality of 7.1% is cited without much comment. Therefore, on the other hand, there has been a lot of improvement.

Of particular interest is the second article on the subject, also from the British Medical Journal—German literature not having been scanned yet. It is from 1888 by Dr. W. J. Tivy about "Notes on Three Cases of Uterine Fibroids under Treatment by Apostoli's Electrical Method" [8]. Already the second available article in the English literature explores alternative treatment options.

The enthusiasm with which this novel—and now largely forgotten—technique is proposed puts the introduction of new treatment approaches into a historical perspective and underlines the need for some form or scientific evaluation. It is important to remember that the prospective randomized trial only became the standard of medical research after the Second World War.

In a second step, diagnosis and therapeutic keywords were combined: "myoma treatment," "fibroid treatment." These terms were further specified using terms such as "randomized trial," "conservative," "hormonal," and "surgical." A large part of available articles was not actually related to our subject matter or involved case reports. Our final selection included not only randomized trials, but also review articles, observational studies, and retrospective studies.

The available—and as always limited—literature that specifically offers prospective randomized data has been previously reviewed by the Cochrane Collaboration. It was our aim to present a balanced but clinically oriented review that focuses on real life data and relates to the everyday experience and the decision-making process surgical gynecologists face in their routine practice.

3. Results

3.1. Medical Treatment. While oral contraceptive pills have been used to treat myoma-related symptoms such as bleeding and dysmenorrhoea, their effect is usually based on their suppression/regulation of the menstrual cycle. The effect of ethinyl-estrogen/progesterone containing pills on myoma growth is less clear. Few authors mention an effect on myoma size. Increasingly, new insights into the molecular biological effects of hormones on leiomyoma cells are being investigated; however, so far no direct therapeutic consequences have emerged. [9, 10].

The same is true for the widely used levonorgestrel intrauterine devices, with the most commonly used being Mirena®. Again, mostly bleeding- and dysmenorrhoea-related symptoms are treated while the actual myoma size remains largely unchanged [11].

Thus, until recently conservative medical treatment focused on symptom control, which is appropriate for a disease that only rarely becomes life-threatening and tends to diminish after menopause. This approach of course does

Table 4: Important surgical questions.

(1)	Should hysterectomy be total or supracervical?
(2)	What is the upper size-limit for laparoscopic hysterectomy?
(3)	Should a salpingectomy always be performed during hysterectomy?
(4)	Is surgery safer with or without in-bag morcellation?
(5)	Is there an upper limit for number of fibroids in laparoscopy myomectomy?
(6)	Which suture technique is superior: extracorporeal or intracorporeal?
(7)	Is intrauterine injection of vasoconstrictive drugs necessary?
(8)	Should the uterine arteries be routinely clipped in laparoscopic myomectomy?
(9)	Should patient be pretreated with Gn-RH-analogs prior to hysteroscopic myomectomy?

not address the problem of observing a potentially large fibroid uterus for another 40 years of life-expectancy after 50, when it increasingly becomes an undiagnosed complex solid pelvic tumor, which of course has implications in a 70-year-old women different from those in a 45-year-old women—particularly when a new doctor assumes the care and responsibility of watching a pathologic growth that has never been histologically evaluated.

Recently, selective progesteron-receptor modulators (SPRMs) such as asoprisnil, ulipristal, and telapristone have been evaluated as therapeutic agents for uterine myomas. [12]. The PEARL I and PEARL II trials have shown the ability of ulipristal acetate not only to control myoma-associated bleeding, but also to significantly decrease myoma size, though there is justified discussion as to how clinically significant this size reduction really is [13].

While ulipristal acetate is not yet available in the United States, it has been a considerable commercial success in Europe, where it is sold under the trade name of Esmya®. The success of this highly innovative medication is due not so much to its ability to decrease myoma size but to its ability to control bleeding symptoms without having many side effects. After the introduction of ulipristal acetate, the use of Gn-RH-analogs for the treatment of symptomatic fibroids, particularly the control of significant bleeding due to fibroids, has almost completely disappeared. Clearly, the known disadvantages of Gn-RH-analogs, that is, the severe postmenopausal-like side effects as well as the known negative effect on subsequent surgery, have led to a swift change in real life medical practice [14].

3.2. Surgical Treatment. Hysterectomy and myomectomy have been the treatment of choice for over 100 years; ever since surgery became safe and feasible. The historical articles mentioned in Material and Method underline this fact. Over the past 20 years, minimally invasive techniques have largely supplanted the open, laparotomic procedures. A large body of published literature has accompanied this technical process, providing scientific evidence of safety and superiority of the minimally invasive approach. Laparotomy is today practised on special clinical cases and in locations, where the necessary technology of laparoscopy is not readily available.

In this context, it is important to mention the sarcoma-morcellation discussion in the United States, which has the potential to roll back years of minimally invasive progress and lead to a recurrence of increased mortality and morbidity due to a return of laparotomy. While conflicting evidence is emerging, the fundamental question remains unanswered and controversial: Does mechanical morcellation affect the biological evolution of the underlying oncologic disease [15–17]? In the United States, for legal reasons, in-bag-morcellation techniques are introduced without a proper scientific evaluation of their complication rates and spilling. Overall, the entire morcellation discussion is clearly legally driven and has many similarities to the proposed association between silicone implants and autoimmune disease in the 1990s. For surgeons and patients a difficult situation has developed and the conclusion of the current discussion is not in sight. It is interesting to note that the possibility of occult sarcoma rarely comes up in association with the conservative treatment options, which, by definition, leave behind the uterine tumor without any diagnosis at all [18].

Key questions need to be answered during surgery for myoma and for hysterectomy. They are summarized in Table 4 and answered in the discussion section.

For the specific diagnosis of submucous, that is, intracavitary myomas, hysteroscopic myomectomy remains the only treatment option. Often, conservative treatment does not work in the long term, while the successful removal of an usually solitary submucous fibroid usually results in a complete resolution of all symptoms. While intramural and subserous myomas can be managed by "watchful waiting," symptom-oriented treatment, or medical intervention (surgical or nonsurgical), the diagnosis of a submucous myoma as the cause of menorrhagia and dysmenorrhoea should lead to immediate scheduling of operative hysteroscopy.

3.3. Conservative, Nonmedical Treatment Options. Radiologically guided arterial myoma embolization was the first nonsurgical, nonmedical treatment approach to fibroid treatment. It was introduced in the late 90s, when no good treatment alternative existed and minimally invasive techniques had not yet become mainstream. At that time, removal of myomas usually meant open surgery, laparotomy, and the primary recommendation of most gynecologists for all women except those clearly desirous of future childbearing ability was hysterectomy.

Understandably, the disadvantages of arterial catheterisation in the groin when compared to laparotomy made this approach seem a viable alternative. [19]. The widespread

Table 5: Treatment options, myoma counseling cascade.

(1)	Diagnostic evaluation: rule out submucous fibroid or nonmyoma diagnosis
(2)	Do nothing: watchful waiting
(3)	Only treat symptoms: bleeding, pain
(4)	Hormonal treatment: oral contraceptive pill, focus on bleeding
(5)	Hormonal treatment: ulipristal acetate
(6)	Fibroid embolization: radiology
(7)	HIFU treatment: radiology
(8)	Laparoscopic evaluation and surgical treatment
(9)	Laparoscopic evaluation and hysterectomy

introduction of minimally invasive surgical techniques leads to a reassessment of the clinical realities of myoma embolization: painful induced necrosis, often leading to unplanned hospitalizations, only very limited shrinkage of fibroids, unclear effect on childbearing, and subsequent need for additional surgical therapy (hysterectomy or myomectomy) [20]. Furthermore, radiation exposure has become an issue with many patients, which might explain why, after initial enthusiasm, this therapeutic approach has lost some of its appeal in recent years.

A novel technique that has found widespread acceptance only recently is the high frequency ultrasound treatment of fibroids, also known as HIFU. As a completely noninterventional treatment, it uses focused ultrasound waves to create thermic coagulation-zones within the myomas, again leading to subsequent necrosis and shrinkage. Two available technologies exist: the more widely used MRI-guided approach and the more advanced ultrasound-guided approach.

The question behind the scientific discussion about whether or not HIFU is an appropriate treatment for fibroids is more general: Does focused high-energy ultrasound have a true medical potential? Will it be the "knife" of the future surgeon? Already, publications of HIFU treatment of prostate cancer, breast cancer, and a variety of other benign or malignant tumors exist [21, 22].

There is little question that in selected patient populations, generally thought to be about 10% of all myoma-patients, HIFU can work. It will lead to necrosis and (partial) shrinkage of fibroids. Just like arterial myoma embolization, it is not an entirely benign procedure: the main complication is thermic injury to bowel, bladder, or, most commonly, the overlying skin. However, generally speaking the complication rate is very low. One disadvantage is the long treatment time, requiring patient to remain immobile in a specific position, sometimes for hours, with ultrasound-guided techniques requiring much less time [23].

4. Discussion

Modern myoma treatment has evolved over more than one hundred years. It involves traditional surgical methods that have been refined though new technological advances: minimally invasive, that is, laparoscopic myomectomy, novel medical treatments, that reflect our increasing understanding of the molecular biologic basics of fibroids as well as completely new approaches such as ultrasound treatment.

Important questions need to be discussed at a very individual level: symptoms, fertility, general attitude, expectations, and age, creating a multifactorial decision-matrix. The available evidence, as reviewed by this article, answers many scientific questions about effectiveness, side effects, long-term outcomes, and possible complications.

Few treatment options have been more thoroughly evaluated than myoma treatment, and, yet, no randomized prospective trial can answer the question: What is the best treatment? This question can only be answered as part of a shared patient-doctor decision-making process. One important aspect of this process is adequate counseling. Table 5 summarizes the counseling-cascade that should be presented, discussed, and documented, to make sure that all options were truly presented to the patient.

The available literature clearly answers many questions. Are minimally invasive procedures safe? In the hands of a skilled surgeon, the answer is "yes." Can nonsurgical interventions be recommended? Yes, they are safe and suitable for selected patients. Should hysterectomy be total or supracervical? Either approach can be chosen, it mostly depends on patient preference. No difference with regard to sexual function or pelvic floor support has been shown [24–27]. What is the upper size-limit for laparoscopic hysterectomy? It depends on the surgeon's willingness to torture him/herself and the OR team. Not everything that is laparoscopically possible makes laparoscopic sense. Should a salpingectomy always be performed during hysterectomy? Prospective data is lacking, but most gynecologic surgeons would counsel in favor of prophylactic salpingectomy [28]. Is surgery safer with or without in-bag morcellation? In the United States, in many hospital settings, unprotected morcellation is no longer allowed. Whether it is safer needs to be shown over the next years. Is there an upper limit for number of fibroids removed in laparoscopic myomectomy? Most surgeons would consider laparotomy when more than five fibroids are involved; however, the final decision depends on surgeon preference, site of the myomas, and patient desire to avoid laparotomy [29]. Which suture technique is superior: extracorporeal or intracorporeal. It depends on surgeon choice. Is intrauterine injection of vasoconstrictive drugs necessary? There is low quality evidence for its benefit [30]

but most experienced surgeons will use it. Should the uterine arteries be routinely clipped in laparoscopic myomectomy? Clipping the uterine arteries requires fairly advanced technical skills. When serious bleeding is expected, it can make an extensive laparoscopic myomectomy laparoscopically feasible [31]. Should patient be pretreated with Gn-RH-analogs prior to hysteroscopic myomectomy? Ideally, visualization should be optimal during intracavitary procedures; that is, no endometrial lining should obstruct the surgeon's view. Gn-RH-analogs can help [32]. In summary, many ways lead to Rome as far as myoma treatment is concerned and surgery remains the most effective and the definitive highway.

5. Conclusion

Presently, the following options exist for effective myoma treatment, starting from the most conservative approach to the most invasive approach: symptomatic treatment with oral contraceptive pills or levonorgestrel-releasing IUDs, ulipristal acetate treatment, HIFU, myoma embolization, surgical myomectomy (hysteroscopic, laparoscopic, open), and hysterectomy. Different factors will affect the patient's choice: personal preference, age, desire for childbearing and future fertility, individual symptoms, and local medical availability of different treatment approaches. Because of the highly heterogeneous clinical situations, prospective randomized trials rarely reflect the individual patient-physician decision. At this point, no superior treatment can be defined. However, all treatment options included in this review have proven their safety and effectiveness and should be discussed with the patient, depending on their availability.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

From Clinical Symptoms to MR Imaging: Diagnostic Steps in Adenomyosis

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Adenomyosis or endometriosis genitalis interna is a frequent benign disease of women in fertile age. It causes symptoms like bleeding disorders and dysmenorrhea and seems to have a negative effect on fertility. Adenomyosis can be part of a complex genital and extragenital endometriosis but also can be found as a solitary uterine disease. While peritoneal endometriosis can be easily diagnosed by laparoscopy with subsequent biopsy, the determination of adenomyosis is difficult. In the following literature review, the diagnostic methods clinical history and symptoms, gynecological examination, 2D and 3D transvaginal ultrasound, MRI, hysteroscopy, and laparoscopy will be discussed step by step in order to evaluate their predictive value in the diagnosis of adenomyosis.

1. Introduction

In the past, adenomyosis was diagnosed when histopathology revealed the disease after hysterectomy. Different publications report a rate of more than 30% of adenomyosis in hysterectomy specimens in premenopausal women undergoing hysterectomy for various indications [1]. However, the age depending incidence of adenomyosis, especially in young patients, so far remains unclear. Present evidence suggests that adenomyosis has a negative impact on female fertility [2, 3]. Salim et al. and Tremellen and Thalluri reported a decrease of pregnancy rates by 50% in women with adenomyosis undergoing IVF [4, 5]. Thalluri and Tremellen showed the negative impact on successful implantation following GnRH antagonists IVF treatment in patients with ultrasound diagnosed adenomyosis [6]. However, Benaglia et al. reported that asymptomatic adenomyosis diagnosed at transvaginal sonography does not impair implantation rates in IVF cycles [7]. Differences in study design, choice of patients and controls, and methods and parameters used to diagnose adenomyosis may explain these discrepancies. Kissler et al. concluded that in patients with intact tubo-ovarian anatomy adenomyosis might be the cause for subfertility [8]. Limited data from uncontrolled studies show that treatment of adenomyosis may improve infertility in women undergoing IVF [9]. Tao et al. showed that GnRH-antagonist cycles have an adverse effect on the outcome, while GnRH-agonist long cycle protocols may improve pregnancy rates and decrease abortion rates [10]. In combination with deep infiltrating endometriosis (DIE), the presence of adenomyosis also plays an important role. Vercellini et al. showed that adenomyosis was associated with a 68% reduction in the likelihood of pregnancy in women seeking conception after surgery for rectovaginal and colorectal endometriosis [11]. Lazzeri et al.

Table 1: Diagnostic methods and their typical findings in adenomyosis.

Diagnostic method	Findings	References
Clinical history and symptoms	Dysmenorrhea, abnormal bleedings, pelvic pain, dyspareunia	[1, 16–19]
Gynecological examination	Uterine and pelvic pain, uterine size and mobility, deep infiltrating endometriosis	[1, 12, 20]
2D transvaginal ultrasound	Heterogeneous myometrium, hyperechoic linear striation in the myometrium, myometrial anechoic cysts, subendometrial microcysts, asymmetrical myometrial thickening, globally uterine enlargement, question mark sign, thickening of the junctional zone, hyperechoic myometrial areas	[21–26]
3D transvaginal ultrasound	JZ (max) > 8 mm, myometrial asymmetry, hypoechoic striation	[26–29]
MR imaging	JZ (max) > 12 mm, high-signal-intensity myometrial spot, JZ (max) to myometrial thickness ratio >40%	[30–34]
Hysteroscopy	Irregular endometrium, endometrial defects, altered vascularization, cystic lesions	[22, 24, 35–37]
Laparoscopy	Uterine enlargement, pillowy resistance, "blue sign," cystic subserous lesions	[22, 38–40]

reported that in 48.7% of patients with DIE also adenomyosis was found. The therapy of DIE reduced the symptoms. But in the group of patients with adenomyosis, the postsurgical result was significantly worse [12]. Thus, in the treatment of endometriosis related pain and/or infertility, it is of importance to know if adenomyosis is a possible cause of the symptoms. Screening for adenomyosis before suggesting surgical or medical treatment procedures may allow identification of subgroups and may lead to individual therapy planning [13]. But so far it remains difficult to diagnose adenomyosis as no reliable diagnostic standard exists. However, different diagnostic methods like clinical examination, transvaginal ultrasound, MRI, and hysteroscopy with guided biopsy have a high sensitivity and specificity in the hands of the skilled examiner. Especially with a standardized 2D-transvaginal ultrasound in combination with clinical symptoms and bimanual examination, considering the recently described sonographic parameters in adenomyosis has the potential to be a reliable, cost-effective, and accessible tool in the diagnosis of adenomyosis.

2. Methods

PubMed search has been conducted using the keywords adenomyosis, hysteroscopy, 2D transvaginal sonography, 3D transvaginal sonography, doppler sonography, elastography, MR imaging and laparoscopy.

3. Results and Discussion

The diagnosis of adenomyosis is difficult, especially in young premenopausal women. Different diagnostic methods offer subtle predictive factors in order to determine adenomyosis. Its combination in daily practice can help to ensure the diagnosis with or without a respective histopathologic proof (Table 1). Usually the clinical symptoms in combination with the result of the gynecological examination guide the way to the suspicion of adenomyosis [14]. In a next step, the transvaginal 2D and 3D sonography considering the typical signs of adenomyosis can confirm the clinical aspects and strengthen the diagnosis of adenomyosis [15]. In some cases, MR imaging can be helpful in order to determine the localization and size of the adenomyotic lesion and differentiate it from fibroids. Hysteroscopy and laparoscopy can then facilitate biopsies or surgical treatment options. In all mentioned steps, the accuracy of the diagnostic methods depends on the experience and skills of the examiner and requires a respective learning curve.

3.1. Clinical History and Symptoms. Adenomyosis is associated with dysmenorrhea, uterine bleeding disorders, chronic pelvic pain, and dyspareunia [1]. Li et al. reported that, in 710 premenopausal patients with adenomyosis, only 4.5% had no symptoms. With a rate of 81.7%, dysmenorrhea was the most common complaint [16]. Krentel described a rate of 60% of adenomyosis in uterine specimens after hysterectomy in a group of patients with the indication dysmenorrhea and bleeding disorders for surgery [17]. Thus, in patients with dysmenorrhea, the presence of adenomyosis should be assumed and determined by further diagnostic steps. However, clinical features in adenomyosis can change in relation to the patients age [18]. In young patients, the symptoms dysmenorrhea and chronic pelvic pain usually are correlated with the possibility of a peritoneal endometriosis and lead to diagnostic laparoscopy. Typical diagnostic imaging features of adenomyosis might be missing in such cases. However, persistent dysmenorrhea after complete laparoscopic resection of extrauterine endometriosis could be a sign for the presence of adenomyosis [19].

3.2. Gynecological Examination. The clinical examination alone cannot detect uterine adenomyosis. In some cases, the uterus might be larger than normal, but the alterations

of the uterine tissue cannot be diagnosed without imaging techniques. However, the bimanual examination can help to estimate uterine or pelvic pain, pain localization, uterine size and mobility, adnexial masses, and the presence of deep infiltrating endometriosis in the retrocervical region like the rectovaginal septum. This is of importance as deep infiltrating endometriosis is correlated with adenomyosis in almost every second case [12]. Thus, the gynecological examination allows more detailed information about severity and complexity of the disease in the planning of medical or surgical treatment [20]. As a next step, clinical history and gynecological examination should be combined with transvaginal ultrasound considering the diagnostic sonographic signs of adenomyosis.

3.3. 2D and 3D Transvaginal Ultrasound. In the last years, transvaginal sonography (TVS) has been described as a diagnostic tool in adenomyosis with a range of sensitivity from 65 to 81% and of specificity from 65 to 100% [21]. Several 2D and 3D features in TVS associated with adenomyosis have been reported in various publications. Di Donato et al. described the nine following parameters as main criteria in the diagnosis of adenomyosis by TVS: heterogeneous myometrium, hyperechoic or hypoechoic linear striation in the myometrium, myometrial anechoic lacunae or cysts, subendometrial microcysts, asymmetrical myometrial thickening of the uterine wall, globally uterine enlargement, the so-called question mark sign, thickening of the junctional zone, and hyperechoic myometrial areas [41–43]. Graziano et al. summarized these parameters in a pictorial review concluding that TVS provides easily recognizable diagnostic signs enabling the diagnosis of adenomyosis by every gynecologist [22]. In a systematic review, Dartmouth concluded that the presence of myometrial cysts, linear myometrial striations, poor delineation of the JZ, and a heterogeneous myometrium raise the probability of the presence of adenomyosis, while anteroposterior uterine asymmetry is not a useful feature [23]. Kepkep et al. reported that subendometrial linear striations have the highest accuracy in the sonographic diagnosis of adenomyosis [44]. A diagnostic accuracy of 75% has been reported for the presence of the question mark sign by Di Donato et al. [41]. In 2006, Dueholm postulated that the diagnosis of adenomyosis is suggested by the presence of three or more of the abovementioned signs [24]. In 2009, Meredith et al. reported a probability of adenomyosis with an abnormal transvaginal ultrasound of 66.2%, while the probability of adenomyosis with a normal transvaginal ultrasound was only 9.1% [45]. Pinzauti et al. showed a significant relationship between the number of 2D-TVS features of diffuse adenomyosis and VAS score for dysmenorrhea. In their observational study, diffuse adenomyosis was found in 34% of 18–30-year-old nulligravid women with regular menstrual cycle and without endometriosis. An asymmetrical myometrial thickening of the uterine walls was the most common TVS feature observed [46]. Dakhly et al. reported a sensitivity of 83.95% and a specificity of 60% of 2D-TVS in the diagnosis of adenomyosis in 292 patients with clinical suspicion of adenomyosis. In combination with hysteroscopic endomyometrial biopsy, the specificity increased to 89% [25]. Exacoustos et al. described the presence of myometrial cysts as the most specific and heterogeneous myometrium as the most sensitive feature in 2D-TVS [26]. Bazot et al. compared transvaginal ultrasound with magnetic resonance imaging and described a sensitivity of 76.4% and a specificity of 92.8% in the diagnosis of adenomyosis with TVS. Myometrial cyst was the most sensitive and specific parameter. In this study, no difference in accuracy was found between 2D-TVS and MRI, but sensitivity was lower with ultrasound in patients with additional uterine myomas [30]. Di Donato et al. reported a sensitivity of 92% and a specificity of 88% of 2D-TVS in a group of 50 patients scheduled for hysterectomy due to symptoms of endometriosis or adenomyosis [41].

Recent studies indicate that 3D-TVS might be superior to 2D-TVS in the diagnosis of adenomyosis [27]. Especially in the evaluation of the junctional zone, which is altered by adenomyosis, the 3D technique allows a more detailed assessment. In 2011, Exacoustos et al. showed a good diagnostic accuracy for adenomyosis by 3D-TVS of the coronal uterine section with evaluation and measurement of the junctional zone [26]. Luciano et al. demonstrated high diagnostic accuracy of 3D-TVS in detection of site and position of adenomyosis in the uterine wall by obtaining targeted biopsies after sonography. The most specific parameters in 3D-TVS were JZ (max) > 8 mm, myometrial asymmetry, and hypoechoic striation. Considering two of the mentioned features, the accuracy of diagnosis reached 90% [28]. Sharma et al. reported a rate of 86% of ill-defined junctional zone in 3D-TVS in patients with adenomyosis. Interestingly the feature central vascularity was found in 93% of adenomyosis lesions in additional Doppler sonography, while leiomyomas showed peripheral vascularity in 89% of the cases. Considering PI, RI, and Vmax, sensitivity was 95.6%, specificity was 93.4%, the PPV was 88.6%, and the NPV was 97.6% in the diagnosis of adenomyosis. Thus, they concluded that additional Doppler sonography can help to diagnose adenomyosis and distinguish it from myomas [29]. Another additional sonographic technique in the diagnosis of uterine tumors is sonoelastography that measures tissue strain and stiffness. In a prospective cohort study, Stoelinga et al. showed that myometrium, myomas, and adenomyosis had different elastographic characteristics and color patterns and thus the technique was able to discriminate the lesions. The agreement with MRI results was excellent [47]. Acar et al. reported an increase of the myometrial stiffness in adenomyosis compared to normal myometrium measured with shear wave elastography [48]. However, this method so far does not play an important role in the diagnosis of adenomyosis. In conclusion, the accuracy of transvaginal ultrasound in the diagnosis of adenomyosis is very variable depending on the selected examination criteria and the observer variation. In different studies, in accordance with the respective actual recommendations, adenomyosis was diagnosed by TVS in the presence of one to three or more sonographic features. In many studies, the imaging result was compared to histopathologic results after hysterectomy. Usually those patients are older than many of the possibly affected

population and therefore likely to be more symptomatic with advanced severity of disease and sonographic and MRI features might be easier to detect than in younger patients. Thus, the study results regarding sensitivity and specificity cannot be easily compared. Considering four apparently similar studies, the reported sensitivity and specificity of 2D-TVS for the diagnosis of adenomyosis range from 87.1% to 57.4% and 97.5% to 60.1% [23]. A consensus statement on sonographic features of the uterus by the MUSA (Morphological Uterus Sonographic Assessment) group summarizes the parameters and the use of terminology in the sonographic description of adenomyosis and uterine myomas [49]. However, a reliable standardized transvaginal ultrasound scheme considering the most specific and sensitive parameters in recent literature should be established.

3.4. Magnetic Resonance Imaging (MRI). MRI is a useful technique in the detection of adenomyosis and especially in the differentiation between adenomyosis and uterine myomatosis. In a prospective cohort observational study, Stamatopoulos et al. described a sensitivity of 46.1%, a specificity of 99.2%, and a positive predictive value (PPV) of 92.3% of MRI in the diagnosis of adenomyosis [31]. Typical MRI parameters in uteri with adenomyosis are the focal or diffuse thickening of the junctional zone, an area of low-signal-intensity in the myometrium, and high-signal-intensity spots in the T2-weighted resonance. Bazot el al. reported a sensitivity of 77.5%, a specificity of 92.5%, and a PPV of 83.8% in a prospective study with 120 patients. Junctional zone thickness (JZ (max)) > 12 mm, a JZ (max) to myometrial thickness ratio >40%, and the presence of a high-signal-intensity myometrial spot were the most specific factors, while JZ (max) was the most sensitive value [30]. Normal junctional zone thickness is considered to be <8 mm [32]. Novellas et al. reported a diagnostic accuracy in adenomyosis by MR imaging of 85%. Junctional zone thickness > 12 mm was the most important finding [33]. In daily practice, the diagnostic tool TVS is more accessible and cost-effective followed by MR imaging and in many cases the accuracy is similar or even higher in TVS, especially when combined with 3D and Doppler. In uncertain cases, MR imaging can be helpful to determine the diagnosis. Adenomyosis also can present as a circumscribed adenomyoma or adenomyotic cystic region or polyp [34]. In these cases, the MRI allows a detailed description of localization and size of the lesion, especially in the preoperative planification for surgical resection of focal or diffuse adenomyosis in infertility treatment. The appearance of adenomyosis in MR imaging also changes under hormonal treatment.

3.5. Hysteroscopy. Diagnostic hysteroscopy is a simple minimally invasive method in order to detect pathologies in the uterine cavity. It can easily be combined with laparoscopy and perturbation of fallopian tubes in patients with endometriosis and or primary or secondary infertility and is a useful diagnostic and therapeutic tool in patients with adenomyosis [35]. In diagnostic hysteroscopy typical findings have been reported in the last years [36]. Molinas and Campo described irregular endometrium with endometrial defects, altered vascularization, and cystic hemorrhagic lesions as possible signs associated with adenomyosis [37]. Superficial openings on the endometrial cavity, hypervascularization, and cystic hemorrhagic lesions were reported as suggestive for adenomyosis by Graziano et al. [22]. However, a pathognomonic feature for adenomyosis in hysteroscopy does not exist. Additionally, hysteroscopy allows the retrieval of targeted endomyometrial biopsies. In transvaginal ultrasound, localization and diameter of the suspicious lesion and its profundity in relation to the thickness of the uterine wall can be described. Thus, a minimally invasive, tissue-sparing biopsy can be obtained as a proof to the disease. In a cross-sectional study with 292 patients clinically suggestive of having adenomyosis, Dakhly et al. investigated the accuracy of endomyometrial biopsy obtained by office hysteroscopy for the histopathologic proof of adenomyosis. Adding hysteroscopic endomyometrial biopsy to the result of TVS improved the specificity from 60 to 89% [24]. Already in 1992 McCausland concluded that hysteroscopic myometrial biopsy can diagnose adenomyosis [50]. The certainty of a positive histopathological result makes it easier to understand the presence of adenomyosis for the patients and facilitates non-evidence-based therapeutic decisions like the use of GnRH analogues or temporary LNG-IUDs in patients with adenomyosis and infertility. In adenomyosis hysteroscopy is not just a diagnostic tool, but also a minimally invasive approach in the treatment of subendometrial and myometrial cystic adenomyomas [51, 52] or polypoid adenomyomas [53] by monopolar or bipolar hysteroscopic resection.

3.6. Laparoscopy. In patients undergoing laparoscopy for peritoneal or deep infiltrating adenomyosis, the uterus can be evaluated during surgery and the suspicion of additional adenomyosis can be substantiated with the laparoscopic uterine appearance. Uterine enlargement, a pillowy resistance of the uterine wall, and cystic subserous hemorrhagic lesions are possible laparoscopic parameters in adenomyosis. Another characteristic finding can be the "blue sign," which describes the color of the adenomyotic tissue during blue dye test [22]. Undirected laparoscopic biopsy techniques without prediagnosed suspicious lesions are not helpful due to unsatisfactory sensitivity and specificity in order to proof adenomyosis histologically. Visible subserous cystic lesions can be resected laparoscopically [38] and focal or diffuse adenomyomas can be treated by laparoscopic adenomyomectomy in order to reduce symptoms [39, 40, 54] and thus biopsies can be obtained.

4. Conclusions

A reliable diagnose of adenomyosis can be made by the combination of clinical history, gynecological examination, and transvaginal 2D and 3D ultrasound. In addition, Doppler sonography and MR imaging might help to determine adenomyosis, especially in cases with combined uterine fibroids. Histologic certainty can be achieved by targeted hysteroscopic biopsy following transvaginal ultrasound with localization of the adenomyotic lesions. Thus, the presence

or absence of adenomyosis can be included in the individual treatment concept of every patient. More detailed prospective studies are needed in order to determine the accuracy of the different diagnostic tools in adenomyosis.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Clinical Study

In-Bag Morcellation as a Routine for Laparoscopic Hysterectomy

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Tissue morcellation during laparoscopic hysterectomy carries the risk of spreading cells from unsuspected malignancy. Contained morcellation inside a bag is supposed to minimize this risk. The present study evaluated routine use of in-bag morcellation during laparoscopic hysterectomy in a consecutive patient cohort ($n = 49$). The system used was More-Cell-Safe (A.M.I. Austria). Median age was 47 (35 to 76) years and BMI 25.1 (18.8 to 39.8). Indications for hysterectomy were fibroids (71.4%), adenomyosis (16.3%), prolapse (8.2%), and bleeding disorders (4.1%). 48 (98%) patients underwent supracervical hysterectomy and 1 (2%) underwent total hysterectomy. No unsuspected malignancy occurred. Median weight of extirpated tissue was 195 g (18 to 1110). Residual tissue and/or fluid in the bag amounted to 29 g (0 to 291). Median overall duration of surgeries was 100.5 min, and median time associated with the use of the bag was 10 min (5 to 28), significantly correlated with uterine volume ($p = 0.0094$) and specimen weight ($p = 0.0002$), but not with patient's BMI ($p = 0.6970$). Technical success rate for contained morcellation was 93.9%. Peritoneal washings after contained morcellation were all negative for malignant or smooth muscle cells.

1. Introduction

Laparoscopic hysterectomy requires special techniques in order to remove the uterine specimen from the peritoneal cavity despite small incisions. In case of supracervical hysterectomy, the main alternative to salvage laparotomy consists in tissue morcellation, which may also become necessary for total hysterectomy specimens when they are too large for being pulled through the vagina entirely. Since 1993, method of choice for tissue morcellation has been power morcellation [1], which came under scrutiny after strong and repeated warnings by the FDA in 2014 [2, 3], indicating the risk for spreading malignant cells during the procedure originating from unsuspected sarcoma mistaken for benign fibroids.

There is an ongoing debate on incidence and significance of the phenomenon, with wide ranges of reported frequencies between 0.02–0.25% referring to unsuspected leiomyosarcoma and 0.13–0.47% to uterine malignancies overall [4–6]. But beside malignant processes, so-called parasitic leiomyoma or peritoneal adenomyosis has been reported as a result of tissue dissemination as well [7–9].

Regardless of the dispute on incidence numbers, international gynecological societies strongly recommend thorough patient information on the potential risks and consent before considering morcellation [4, 5, 10]. Beyond counseling, risk stratification might improve patient selection, but despite upcoming recommendations [4] valid concepts are missing so far.

Another strategy to optimize patient safety, simultaneously maintaining the proven advantages of minimal invasive hysterectomy [11, 12], would consist in improving surgical techniques of morcellation. A promising approach could be contained morcellation inside a bag in order to prevent spilling of uterine tissue or cells [13, 14]. In this regard, we recently introduced a new system for in-bag morcellation, which proved feasibility and a preventive effect in both experimental and clinical pilot settings [15, 16].

The aim of the present work was to report our continued experience using the new system in clinical routine application during laparoscopic hysterectomy.

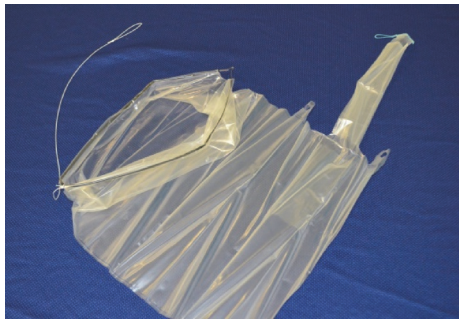


Figure 1: More-Cell-Safe bag (A.M.I. Austria) for contained power morcellation: material polyurethane, feed sizes of 340 × 250 mm, capacity 2.5 liters; large opening of 160 mm for specimen placement and morcellator access and small tubular opening for optic trocar access.

2. Materials and Methods

2.1. Patients. Experiences with contained morcellation during laparoscopic hysterectomy in $n = 49$ consecutive patients were retrospectively analysed in this observational cohort study after obtaining CE approval. Informed consent was obtained from all patients. Counseling included information on the surgical techniques, alternatives, risks, and benefits of laparoscopic hysterectomy as well as on power morcellation risks. Possible spread of undetected malignancy was quoted according to the statement of the DGGG [5].

2.2. Operative Procedure. According to the description in our preceding pilot study, the procedure started with total or supracervical laparoscopic hysterectomy. A multiport approach was used with a 11 mm umbilical trocar for optic (0°), suprapubic, and two lateral 6 mm trocars. After completing the hysterectomy, the More-Cell-Safe system (A.M.I. Austria) for contained power morcellation (Figure 1) was introduced into the peritoneal cavity via either a 12 mm disposable plastic sheath (MCS-Port, A.M.I. Austria) or a 13 mm reusable metal trocar (Karl Storz, Germany). The polyurethane bag (More-Cell Bag, A.M.I. Austria) has feed sizes of 340 × 250 mm and a capacity of 2.5 liters. It has two openings measuring 160 and 16 mm. The large opening serves as a specimen placement and morcellator access suprapubically. The small opening allows optical trocar insertion at the umbilical site. The outer part of the tubular bag opening is everted to protect it from contamination by spread cells during use. In order to allow the bag to be introduced through the suprapubic trocar, it is delivered folded into a sleeve, that has to be stripped while inserting into the bag. First-generation bags were rolled instead of being folded. These were applied in 11 cases. Second-generation bags are folded allowing self-opening of the large mouth of the bag into the peritoneal cavity after insertion. Those were applied in all consecutive cases (12–49).

An 11 mm sleeve (Visi-Shield) covers the optic in order to prevent cell contamination during in-bag use. The shield is disposed at the end of morcellation before further use of the optic inside the peritoneal cavity.

After inserting the bag into the peritoneal cavity, the specimen was placed into the bag with the help of grasping forceps using the lateral trocars. For larger specimen handling, a third instrument was applied using the suprapubic access port. After positioning the specimen, the large mouth of the bag was pulled out suprapubically with help of a retrieval thread and simultaneously the respective port removed. The tubular bag opening was now exteriorized through the umbilical access while removing the 11 mm optic trocar.

At this point, the umbilical fascia was enlarged in order to allow entering the larger trocar into the bag. Trocar size is determined by the Visi-Shield diameter requiring at least 12 mm trocar to allow its passage and adequate gas flow between shield and trocar wall. Fascia enlargement was performed bluntly digitally in the first 9 cases and with sharp cutting with scissors under external vision in the 40 consecutive cases. For optic trocar access to the bag, a 12 mm blunt disposable trocar (Versaport, Covidien Medtronic) was used in the first 17 patients, and in all consecutive patients a 13 mm reusable blunt tipped metal trocar was used (Karl Storz, Germany). A pseudopneumoperitoneum was now established inflating the bag via the umbilical trocar and the optic reentered covered by its protective shield. The morcellator (Rotocut G1, Karl Storz Germany, 12 or 15 mm according to the surgeons preference) was then entered bluntly into the bag at its suprapubic opening and electromorcellation started in a contained, but otherwise unchanged technique (Figure 2). In case of total hysterectomy, vaginal closure was performed prior to morcellation.

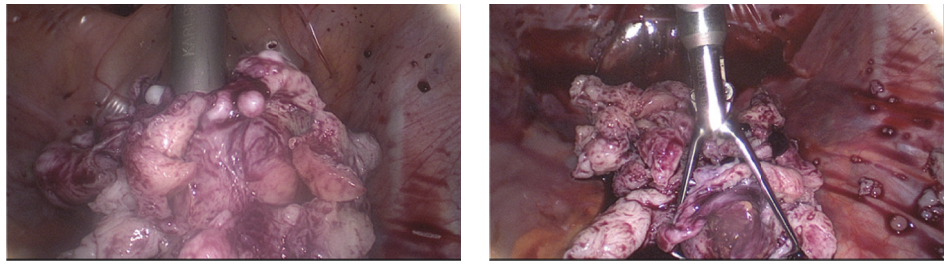
After completion, both morcellator and optic were withdrawn from the bag. Visi-Shield and optic trocar were disposed, the everted tubular part of the bag was unrolled, and the bag was securely closed by two knots. Now, the bag was removed by manually pulling it towards the suprapubic site. For continued laparoscopy, the previously removed 11 mm optic trocar and the optic without shield was reinserted.

2.3. Parameter and Statistical Analysis. Patient baseline characteristics were recorded including age, BMI, history of previous surgery, and preoperative findings including transvaginal ultrasound measurements and indication for surgery.

Procedural parameters were recorded as type of hysterectomy, eventual complementary surgery, and duration of surgery, differentiated into overall procedure time, times associated with the use of the bag, and morcellation time. Overall resected tissue weight was calculated from measured weights of morcellated specimen and residual tissue or fluid inside the bag after removal.

Complications were recorded as intra- or postoperative ones, and duration of hospital stay was registered from surgery to discharge.

Feasibility of in-bag morcellation was determined as intraoperative technical success rate defined as successfully completed contained morcellation procedure including proof of bag integrity after removal by visual inspection and blue stain fluid filling. Additional qualitative parameter was bag handling, adequate pseudopneumoperitoneum, in-bag visualization, and morcellation performance as assessed by the surgeon.



(a) (b)

Figure 2: (a/b) Technique of contained in-bag power morcellation of a supracervical hysterectomy specimen using More-Cell-Safe (A.M.I., Austria).

Table 1: Indications for hysterectomy.

Symptomatic fibroids	35 (71.4%)
Adenomyosis	8 (16.3%)
Prolapse (combined with cervicosacropexy)	4 (8.2%)
Bleeding disorders (dehiscent cesarean scar)	2 (4.1%)

Table 2: Patient and specimen characteristics.

	Median	Range
Patient age	47 years	35–76
BMI	25.1	18.8–39.8
Uterine volume (ultrasound)	350 cm^3	36–2016
Weight of extirpated tissue	195 g	18–1110
Weight of morcellated tissue	170 g	18–819
Residual tissue/fluid in the bag	29 g	0–291

Postoperative histology was registered and compared to preoperative findings. In order to evaluate potential cell spillage from morcellated tissue, cytology was analysed for the presence of smooth muscle cells from peritoneal washings taken at the end of the surgical procedure.

Statistical analyses were performed using GraphPad software with descriptive calculations of median and minimum to maximum range, mean, and 95% confidence interval. Linear regression analysis was performed to describe influence factors on bag associated duration of surgery.

3. Results

3.1. Patient Baseline Characteristics (Tables 1 and 2). Median age was 47, ranging from 35 to 76 (mean 48.3; 95% CI 45.93–50.64). Patient BMI ranged from 18.8 to 39.8 with a median at 25.1 (mean 26.7; 95% CI 25.04–28.41).

Only 24 (49%) patients had no previous abdominal surgery. The others had undergone one or more previous surgeries, among these laparoscopic interventions in 18 (36.7%) cases (myomectomy, endometriosis, ovarian cystectomy or ovariectomy, ectopic pregnancy, tubal ligation, cholecystectomy, and sigma resection), cesarean sections in 10 (20.4%) cases, and open surgery in 8 (16.3%) cases (endometriosis, appendectomy, cholecystectomy, and adhesiolysis for bowel obstruction).

Table 3: Duration of surgery, morcellation, and bag application.

	Median	Range
Overall duration of surgery	100.5 min	55–239
Overall time of bag use (in/out)	19.5 min	8–82
Morcellation time	9 min	2–54
Total time associated with bag use	10 min	5–28
Bag preparation time before morcellation	8.5 min	4–26
Bag removal time	1 min	0–8

Indications for hysterectomy were symptomatic fibroids in 35 (71.4%) cases (7 isolated, 28 multiple myoma), adenomyosis in 8 (16.3%) cases, prolapse in 4 (8.2%) cases (combined with cervicosacropexy), and bleeding disorders in the presence of dehiscent cesarean uterotomy in 2 (4.1%) cases. Three (8.6%) of the 35 myoma patients were pretreated with ulipristal acetate.

Median uterine volume based on transvaginal ultrasound measurement was 350 cm^3 (range 36 to 2016; mean 515.2; 95% CI 390.05–640.28).

3.2. Procedural Parameter (Table 3). Scheduled laparoscopic hysterectomy was performed in all patients without intraoperative complications. 48 (98%) underwent supracervical hysterectomy and 1 (2%) underwent total hysterectomy.

All patients underwent additional interventions (46 salpingectomy, 1 ovarian cyst removal, 4 endometriosis resection, and 4 cervicosacropexy) besides hysterectomy, which were however performed before in-bag morcellation in all cases except one umbilical hernia repair. Remarkably, in 2 of the three cases after previous laparoscopic myomectomy, there were several parasitic myoma cases. All were removed with unsuspicious histological results.

Median overall duration of surgeries was 100.5 min (range 55 to 239; mean 110.4; 95% CI 97.45–123.38). The median overall time frame of bag use from insertion to removal was 19.5 min (range 8 to 82; mean 24.4; 95% CI 16.85–31.97). Morcellation time ranged from 2 to 54 min with a median of 9 min (mean 12.1; 95% CI 7.15–17.12). The time associated with the use of the bag (in total, before and after morcellation) was 10 min (median; range 5 to 28; mean 12.3; 95% CI 9.23–15.31). There was a significant correlation with uterine volume (p =

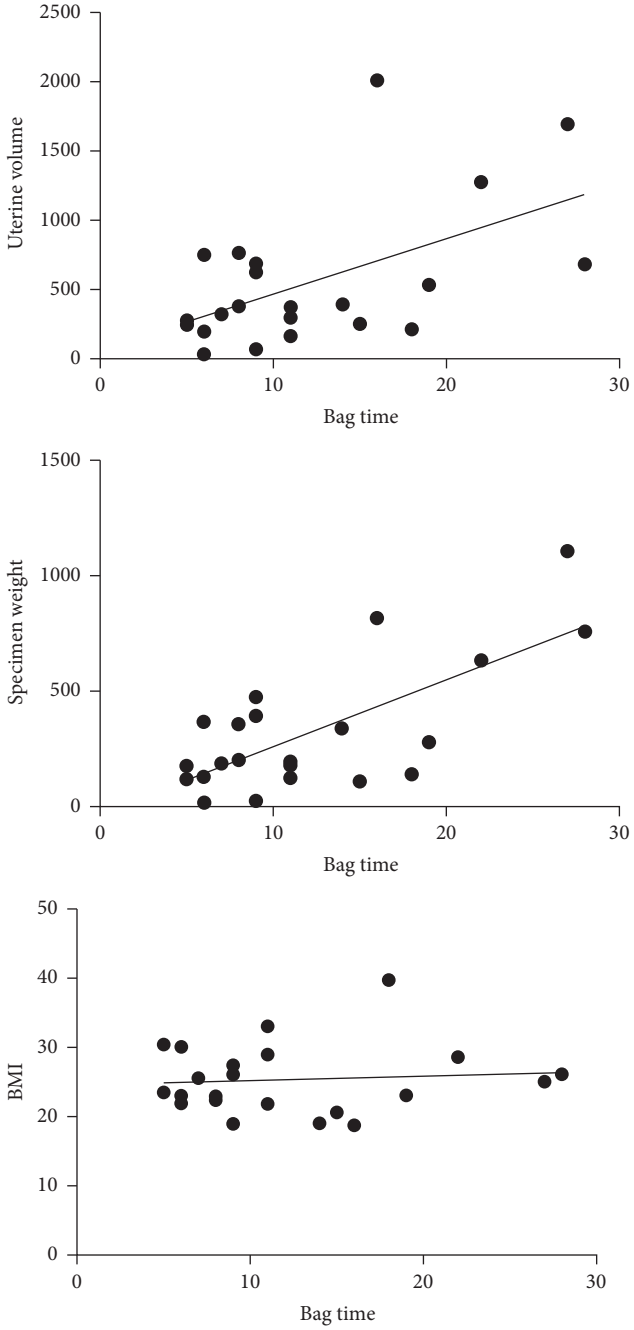


Figure 3: Linear regression analysis showing bag associated time during surgery significantly correlated with uterine volume ($p = 0.0094$) and specimen weight ($p = 0.0002$), but not with patients BMI ($p = 0.6970$).

0.0094) and specimen weight ($p = 0.0002$), but not with patient's BMI ($p = 0.6970$) (Figure 3).

Inserting and preparation of the bag including specimen placement until start of morcellation took 8.5 min (median; range 4 to 26; mean 11.0; 95% CI 8.33–13.67). Removal of the bag after morcellation was performed in 1 min (median; range 0 to 8; mean 1.3; 95% CI 0.53–2.01).

Median overall weight of extirpated tissue was 195 g ranging from 18 to 1110 (mean 269.7; 95% CI 204.20–335.27).

Table 4: Technical feasibility of in-bag morcellation.

Successful and bag intact	46 (93.9%)
Bag defect	3 (6.1%)
Findings in cases of defect bag	(i) 3 mm tear at tubular part due to shearing by the umbilical trocar (too small fascia incision) (ii) Bag ruptured during forced extraction (calcified myoma 50 mm remaining in the bag) (iii) Bag ruptured during forced extraction (residual piece of myoma 30 mm ignored)

From this, morcellated tissues had a median weight of 170 g (range 18 to 819; mean 250; 95% CI 191.41–308.59). Residual tissue and/or blood that remained in the bag and then removed at the end of the procedure amounted to 29 g (median; range 0 to 291; mean 47.8; 95% CI 15.60–80.10).

3.3. Clinical Complications and Duration of Hospital Stay. There were no intraoperative clinical complications. Postoperatively, one patient developed a fever of unknown origin but was treated successfully with antibiotics. Median duration until discharge from the hospital was 3 days (range 2 to 11; mean 3.3; 95% CI 2.91–3.66).

3.4. Feasibility of In-Bag Morcellation (Table 4). Contained morcellation was performed successfully and intact bag after removal in 46 of 49 cases resulted in a technical success rate of 93.9%.

In 3 (6.1%) cases bags appeared not intact after the procedure. One bag showed a 3 mm tear at its tubular part during postprocedural extracorporeal stain fluid filling test. Pattern and localisation of the lesion as well as documented technical problems during umbilical trocar insertion lead to the assumption of shearing by the trocar passing through a too small fascia incision. A second bag was first punctually damaged with the morcellator forceps before morcellation, removed, and replaced by another bag, but this finally ruptured during forced extraction with an inside remaining calcified 5 cm myoma not passing through an inadequate suprapubic incision. Comparably, the third bag, which resulted in defect, ruptured during forced extraction because of an ignored residual piece of myoma of 30 × 15 × 15 mm.

Despite successful procedures, handling difficulties occurred in 8 (16.3%) cases. In two cases, the surgeon decided to remove and replace the initial bags because they were twisted after insertion to the peritoneal cavity and specimen placement was not possible. In both cases, first-generation bags were applied; procedures were successful during second attempt. In a third case, the bag was perforated with the umbilical trocar during insertion. The perforation occurred before morcellation and was immediately detected when the optic was introduced, showing the peritoneal cavity outside the bag. The bag was removed and replaced. The second attempt was then completely successful after having

enlarged the umbilical fascia opening. A fourth case also required change of the bag because of an apparent defect at the tubular segment after pulling it through the umbilical trocar before even starting the in-bag procedure. In the fifth and sixth case with handling difficulties, several attempts of optic trocar insertion into the bag were necessary and only successful after adequately enlarging the fascia incision. In two further difficult cases, it was the surgeon who forgot to strip the sleeve from the bag during initial insertion, which made complete removal and reinsertion of the bags necessary.

There were no difficulties regarding pseudopneumoperitoneum and during actual morcellation. Once the optic trocar was adequately positioned, a pseudopneumoperitoneum could be established regularly in all cases. This applied as well for the defect bag presumably damaged by the optic trocar prior to morcellation. In-bag visualization was not impaired and allowed regular power morcellation in all cases. Median morcellation time was 9 min (range 2 to 54; mean 12.1; 95% CI 7.15 to 17.12).

3.5. Postoperative Histology and Results of Peritoneal Washings. Fibroids were found in 35 cases, sometimes associated with adenomyosis. Adenomyosis alone was described in 11 cases. In three cases, specimen did not show pathology except dehiscence of a former cesarean uterotomy scar in 2 instances. Histology confirmed the clinical suspicion in 45 (91.8%) cases. In 1 case an adenomyoma had been mistaken for a fibroid, and in 3 (6.1%) cases histology revealed a fibroid (1) and adenomyosis (2) sonographically were not detected. Cases of unsuspected malignancies did not occur.

Cytology from the peritoneal washings showed mesothelial cells and/or leucocytes, erythrocytes, and macrophages in all examined cases but was negative for malignant or smooth muscle cells each time.

4. Discussion

Technical feasibility of in-bag power morcellation using the setting here applied had previously been shown in a small pilot series [16]. Data from the present collection of 49 consecutive patients were gathered in order to prospectively examine suitability for use in clinical routine. In fact, enclosed patients represent an unselected cohort of women at varying age, BMI, medical history, and indications for hysterectomy.

Technical success was achieved under these conditions in 93.9%, confirming our pilot results. The absence of smooth muscle cells in all peritoneal washings suggests effective prevention against spilling of cells from the morcellated tissue [15, 17].

The occurrence of three failure cases (6.1%) indicates a remaining risk potential that needs being addressed during informed consent. Analysis of the cases reveals the surgeon's impact on outcome. Restricting the incision of the fascia too much at the umbilical trocar site was not only the main reason for handling difficulties during bag preparation, but also responsible for one of the failure cases with a trocar associated shear lesion of the bag. Bag ruptures occurred only as a consequence of forced extraction in the presence of larger in-bag residuals. Meticulous removal of morcellated tissue from the bag and avoiding force during bag extraction will make bag rupture less likely. In case of tissue remnants which are resistant to morcellation, such as a calcified myoma in one of our cases, adequate abdominal wall incision is mandatory.

Small residual tissue pieces and fluid in the bag, however, do not interfere with appropriate extraction. In our series, they were regularly noted with a median weight of 29 g (range 0 to 291 g). Anapolski et al. [18] reported 12.1 g (range 7 to 19 g) from a pilot study using a different type of bag. Saving time and effort to collect these fragments and rinse the peritoneal cavity may be a positive side-effect of in-bag versus uncontained morcellation.

Nevertheless, application of a bag system consumes time, which was reported to prolong surgery by 20–30 min as compared to retrospective controls with uncontained morcellation [14, 19, 20]. In the present study, median total time associated with the bag use was only 10 min, confirming the positive experience from our pilot work [16]. It ranged from 5 to 28 min, which was significantly correlated with uterine size, ranging from 18 to 1110 g (median 195 g). The most time consuming stage was inserting the bag, placing the specimen, and preparing for morcellation with a median proportional time span of 8.5 min versus only 1 min to remove the bag afterwards. Time specifications in different studies must be compared with caution because of their correlation with specimen sizes in the respective cohorts. Nevertheless, two recent studies using different systems [18, 21] came to slightly longer, but essentially comparable results with 10.5 and 12.5 min preparation time for in-bag morcellation, thus increasing acceptability for clinical routine.

In contrast to our pilot experiences [16], uterine size was not limiting applicability of contained morcellation in this series, though the largest specimen weighed 1110 g. Despite the surgeon's subjective impression, there was no statistically detectable correlation of difficulties, measurable in procedure duration, with patient's BMI. Problems in handling occurred with first-generation bags, which did not open properly. This problem was solved by introducing differently folded second-generation bags, providing easier access for specimen placement. The importance of adequate umbilical fascia incision has already been pointed out. Once, blunt trocar access to the bag interior was successfully established, the actual morcellation process was assessed unhindered and not prolonged under the circumstances of the contained setting.

Technical alternatives consist in vaginal, single-site, or manual open concepts for in-bag morcellation [22–26]. Vaginal access would have been possible for only one of our patients undergoing total hysterectomy, while it was not applicable for all others, operated upon supracervically. Single-site techniques would require a major change of our clinical routine but have to be taken into consideration, as recently the FDA allowed marketing of a bag for contained morcellation using single-site access [27]. Manual in-bag morcellation requires appropriate incisions of the abdominal wall and abandons power morcellation in favor of the scalpel but represents a practicable alternative with the advantage of direct external visual control.

5. Conclusions

The technique presented here allows in-bag power morcellation during laparoscopic hysterectomy in a usual multiport approach with proven feasibility. Preventive effectiveness against spilling from morcellated tissue is suggested by reproducible results of negative peritoneal washings. The promising single center data of this study will now need confirmation in a prospective multicentric approach.

Conflicts of Interest

Stefan Rimbach declares receiving royalties from A.M.I.; Miriam Schempershofe declares no conflicts of interest regarding the publication of this paper.

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Review Article

Myomas and Adenomyosis: Impact on Reproductive Outcome

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Among uterine structural abnormalities, myomas and adenomyosis represent two distinct, though frequently coexistent entities, with a remarkable prevalence in women of reproductive age. Various mechanisms have been proposed to explain the impact of each of them on reproductive outcome. In respect to myomas, current evidence implies that submucosal ones have an adverse effect on conception and early pregnancy. A similar effect yet is not quite clear and has been suggested for intramural myomas. Still, it seems reasonable that intramural myomas greater than 4 cm in diameter may negatively impair reproductive outcome. On the contrary, subserosal myomas do not seem to have a significant impact, if any, on reproduction. The presence of submucosal and/or large intramural myomas has also been linked to adverse pregnancy outcomes. In particular increased risk for miscarriage, fetal malpresentation, placenta previa, preterm birth, placenta abruption, postpartum hemorrhage, and cesarean section has been reported. With regard to adenomyosis, besides the tentative coexistence of adenomyosis and infertility, to date a causal relationship among these conditions has not been fully confirmed. Preterm birth and preterm premature rupture of membranes, uterine rupture, postpartum hemorrhage due to uterine atony, and ectopic pregnancy have all been reported in association with adenomyosis. Further research on the impact of adenomyosis on reproductive outcome is welcome.

1. Introduction

Embryo implantation into the endometrial cavity has been long believed to be mainly driven by endometrial receptivity and to a lower extent by the embryo itself. In this context, impaired endometrial receptivity accounts for two-thirds, whereas embryo quality, in terms of both morphology under the microscope and genetic composition, accounts for one-third of implantation failures [1, 2]. Therefore the role of the endometrium in adverse reproductive outcome should not be disregarded. In this respect, endocrine disorders, inherited and acquired thrombophilias, immunologic abnormalities, and chronic inflammation may be responsible for reduced endometrial receptivity. Structural abnormalities, either congenital such as Mullerian anomalies or acquired ones, such as endometrial polyps, intrauterine adhesions, myomas, and adenomyosis, may compromise embryo implantation following both natural conception and assisted reproduction technologies.

Besides an adverse impact on implantation, both myomas and adenomyosis may interfere by various means throughout the duration of pregnancy and affect the obstetrical outcome [3–11].

2. Uterine Myomas

Uterine myomas, also called leiomyomata, fibroids, fibromyomas, leiomyofibromas, and fibroleiomyomas, are the most common benign uterine tumors. Evaluation by ultrasound reveals the incidence of fibroids as high as 60% by age of 35 years in African-American women and 40% in Caucasian women. The incidence increases to 80% and 70% by age

50 of years, respectively [12]. Thereby, race along with age represents risk factors for myoma development. Interestingly, race is associated with myoma growth rate, given that women of African descent hold a relatively constant rate throughout reproductive life, whereas in Caucasian women myomas keep up a faster growth rate until 35 and a slower one after the age of 45 [13]. Early menarche, nulliparity, caffeine, and alcohol consumption, obesity, and high blood pressure have all been found to increase the risk, whereas smoking, possibly implicated in relative alteration in estrogen metabolism, has been shown to decrease the risk of developing fibroids [14–21].

The pathogenesis of myomas is considered multifactorial. A somatic mutation in a single smooth muscle cell of the uterus is the triggering event, which explains the monoclonal origin of these tumors [14]. However, genetic and epigenetic factors, including steroid hormones, growth factors, cytokines, and chemokines, are also implicated in the development and growth of myomas [20, 22]. Although initially significant attention had been paid to estrogens, nowadays, progesterone and its receptors (PR-A and PR-B) are believed to play a key role in myoma growth, modulating the expression of growth factor signaling proteins and, among others, regulating genes associated with proliferation, apoptosis, and differentiation [14, 20].

Anatomically, myomas are monoclonal tumors expanding, as they grow, between normal myometrial cells creating a pseudocapsule, which consists a fibro-neurovascular bundle, which surrounds the fibroid and separates it from healthy myometrium [23]. Basically, thickened collagen fibers and blood vessels form a vascular ring, which has been described as the "ring of fire" by color Doppler, whereas by conventional grey scale ultrasonography forms a hyperechogenic ring around the myoma [23, 24]. Accumulating evidence supports the importance of this pseudocapsule in secreting, neurotransmitters, and neuropeptides, such as substance P (SP) and vasoactive intestinal peptide (VIP) as well as other molecules all of which are implicated in wound healing [25–27].

Various systems have been proposed so far to describe myomas. Still, none of them takes into account all the parameters, which figure out the heterogeneity of these tumors. Traditionally, based on their location in relationship to the endometrial cavity, myomas are classified as submucosal, intramural, or subserosal [28–30]. The FIGO classification, introduced by Munro and colleagues in 2011, is based on the relationship of the fibroid with the uterine wall [31]. According to this classification, nine types of myomas have been described, from type 0 to type 8, the last one representing fibroids, which cannot otherwise be classified. For a subset of fibroids, two numbers may be applicable, the first one referring to the relationship with the endometrium and the second one with the perimetrium. This possibility can indirectly imply the size of a myoma, which for instance extend throughout the uterine wall protruding into the uterine cavity and concurrently distort the outline of the uterus (types 2–5) (Figure 1). Still, the size, the number, and the exact location the fibroids in relationship to the tubal ostium or the cervix are not taken into account into the classification.

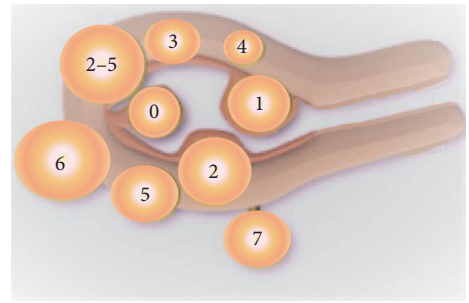

Figure 1: FIGO classification of myomas. FIGO classification system of myomas introduced by Munro and colleagues in 2011 [31] is based on the relationship of the fibroid with the uterine wall. According to this classification, type 0 to type 8, the last one representing fibroids, which cannot otherwise be classified, have been proposed, whereas for a subset of fibroids, two numbers may be applicable, the first one referring to the relationship with the endometrium and the second one with the perimetrium. This possibility can indirectly imply the size of a myoma, which, for instance, extends throughout the uterine wall protruding into the uterine cavity and concurrently distorts the outline of the uterus (type 2–5). Type 0: pedunculated intracavitary. Type 1 submucosal < 50% intramural. Type 2: submucosal ≥ 50% intramural. Type 3: entirely intramural, contacting the endometrium. Type 5: subserosal ≥ 50% intramural. Type 6: subserosal < 50% intramural. Type 7: subserosal pedunculated. Type 8 (not shown in the figure): others, that is, cervical, originating from the round ligament or parasitic.

Myomas are often asymptomatic and are diagnosed in routine ultrasound scan performed for other indications. Symptomatic myomas are associated with abnormal uterine bleeding (menorrhagia and/or metrorrhagia) pelvic pain due to myoma degeneration or torsion of a pedunculated myoma and pressure to adjacent organs, such as the bladder (urgency, frequency, or incontinence), ureters (hydronephrosis), pelvic veins (discomfort and pelvic pain), and rectum (constipation and tenesmus) [32–34].

Myomas can also have an adverse effect on reproductive outcome either by impairing fertility or by complicating the course of and the completion of a pregnancy.

2.1. Myomas and Infertility. Although myomas are present in 5–10% of infertile women, they present as a sole cause of infertility only in 2-3% [35], which means that hardly up to 60% of myomas may cause infertility [34].

Fertility impairment due to the presence of fibroids has been attributed to various mechanisms (Table 2).

Distortion of the uterine cavity, rendering the endometrial contour anomalous, may compromise implantation potential. Furthermore, sperm transport may be hampered by an enlarged and deformed fibroid uterus, whereas cervical displacement may hinder sperm passage into the cervical canal. The presence of myomas may also alter myometrial contractility, which in turn may compromise sperm progression into the female reproductive system. Alteration to the endometrial and myometrial blood supply due to

underlying myomas may also interfere with both uterine contractility and implantation, whereas retained menstrual efflux due to a deformity of the uterine cavity may interfere with both sperm transport and implantation. Deviation or obstruction of the tubal ostia may compromise tubal patency and alteration of the tubo-ovarian anatomic relation may impede ovum collection from the fimbrial end following ovulation. Finally, a chronic inflammatory reaction to the adjacent endometrium, due to the presence of myomas, has been suggested to alter endometrial milieu [30, 34–41].

In fact, the closer the myoma to the endometrial cavity the worse the impact to the overlying endometrium as it has been shown that myomas lying close or in contact with the endometrial surface are associated with histologic alterations, which are known to impair implantation. In fact, endometrial atrophy, ulceration, elongation, and distortion of the endometrial glands, cystic glandular hyperplasia, polyposis, and endometrial venule ectasia have all been reported in the endometrium adjacent to the myoma. Interestingly, endometrial atrophy and ulceration are often evident even on the distal endometrium lying on the opposite uterine wall, probably due to a mechanical effect [30, 42–44].

In a study assessing the effect of uterine leiomyomas on the endometrium using molecular markers of endometrial receptivity, a decrease in HOX gene expression throughout the endometrium and not simply over a submucosal myoma was found. This observation implies that impairment of fertility may be attributed to a global effect and not simply a focal change of the endometrium overlying the myoma [45].

Mechanisms associated with fertility impairment in the presence of myomas frequently coexist, depending on their size, number, and location. However, in assisted reproduction technologies (in vitro fertilization), access of the ejaculated sperm to the cervical canal and sperm transport as well as tubal patency are irrelevant; therefore mechanisms that interfere with the implantation process may have a prominent role [30, 40].

Subserosal myomas, either sessile or pedunculated, distorting the outer uterine contour, do not seem to have a significant impact on fertility potential [36, 40, 46, 47]. Despite the fact that a recent systematic review and meta-analysis of controlled studies found that the presence of fibroids irrespective of their location significantly lowers implantation, clinical pregnancy, and ongoing pregnancy/live birth rates, when the analysis was restricted to subserosal myomas, no difference was observed for any of these endpoints. Therefore, subserosal myomas do not seem to affect fertility outcomes, and their removal does not confer any benefit [47].

The effect of intramural myomas on fertility is still somehow controversial, probably due to methodological limitations, but it has gained increased interest especially in the era of assisted reproduction. It was believed initially that myomas not protruding into the intrauterine cavity are not related to infertility; however, neither the number nor the size of the myomas was taken into account.

Several systematic reviews and meta-analyses have looked at this issue [36, 40, 46–48].

In 2001, Pritts failed to demonstrate an adverse effect of intramural fibroids on fertility in women undergoing assisted reproductive technologies (ART), thereby arguing against surgical intervention [46]. However, four years later, in 2005, Benecke and colleagues reported a negative impact of intramural fibroids on pregnancy rate in ART cycles [40]. In line with Benecke and colleagues, Somigliana and colleagues in an updated meta-analysis in 2007 found an adverse effect of intramural fibroids on ART outcome, in terms of clinical pregnancy and live birth rates [36, 49]. In this context, a systematic review and meta-analysis performed by Pritts and colleagues in 2009 demonstrated that intramural fibroids were associated with decreased implantation, clinical pregnancy, and ongoing pregnancy/live birth rates and higher miscarriage rates [47]. When only prospective studies were evaluated in this meta-analysis, all the aforementioned endpoints, but clinical pregnancy rates, were statistically significant. Finally, when only studies using hysteroscopy to evaluate the intrauterine cavity were assessed, the only significant impact of myomas was documented on implantation rates. It is noteworthy that this meta-analysis included both women undergoing assisted reproduction by any means (in vitro fertilization [IVF], intracytoplasmic sperm injection [ICSI], egg donation and/or embryo recipient program, and intrauterine insemination) and women attempting spontaneous conception. Subsequently, a systematic review and meta-analysis, Sunkara and colleagues focused on the effect of intramural myomas on fertility. They examined only intramural fibroids in respect to the outcome of in IVF [48]. They noticed that intramural fibroids, which by definition did not distort endometrial cavity, were associated with lower clinical pregnancy and live birth rates. However, when they focused their analysis on prospective studies only, they documented an adverse effect solely to live birth rates.

It is obvious that the exact location of an intramural fibroid may also determine its impact on fertility potential; that is to say, a fibroid lying on the cornual end or near the cervix may compromise sperm migration and thus fertilization.

Several efforts have been made to relate the size of an intramural fibroid with reproductive outcome. A cut-off of 2.85 to 7 cm for maximum myoma diameter has been assessed in the literature so far, yielding opposing results [50–54]. Although a recent retrospective cohort study suggested that intramural fibroids greater than 2.85 cm in diameter may negatively affect delivery rates in women subjected to IVF/ICSI treatment, accumulating evidence suggests that a diameter above 4 cm should be probably considered clinically significant from a reproductive aspect [52, 55].

In respect to submucosal myomas, the literature is quite clear. Current evidence highlights their detrimental effect on fertility. The FIGO and the ESGE classifications describe three types of submucosal myomas. Types 0, 1, and 2, of FIGO correspond to types 0, I, and II of ESGE and represent myomas being pedunculated and thus protruding entirely into the intrauterine cavity, sessile with less than 50% myometrial extension and sessile with more than 50% myometrial extension, respectively [56].

Current evidence based on available systematic reviews and meta-analyses, which have looked at the effect of submucosal myomas on fertility [36, 37, 40, 46, 47], all agree that submucosal myomas exert a detrimental effect on reproductive outcome. In a systematic review and meta-analysis conducted by Pritts, in women undergoing IVF, the presence of submucosal fibroids was associated with lower implantation (RR 0.28; CI 0.10–0.72) and pregnancy rates (RR 0.30; 95% CI 0.13–0.70) as compared with infertile controls devoid of fibroids. Surgical removal of these fibroids resulted in increased pregnancy rates (RR 1.72; 95% CI 1.13–2.58) and restored live birth rates (RR 0.98; 95% CI 0.45–2.41) [46]. A year later, Donnez and Jadoul reviewed the literature and ended up with a conclusion that although clear evidence is lacking, it seems reasonable that myomas distorting intrauterine cavity impair implantation and pregnancy rates in ART cycles [37]. In 2005, Benecke and colleagues again reinforced the aspect of a detrimental effect of submucosal fibroids on pregnancy rates in women subjected to ART [40] and in 2007, Somigliana and colleagues reported an adverse effect of submucosal myomas on ART outcome in terms of clinical pregnancy (RR 0.3; 95% CI 0.1–0.7) and live birth rates (RR 0.3; 95% CI 0.1–0.8) [36]. This was also the case in the systematic review and meta-analysis performed by Pritts and colleagues in 2009, in an unselected population undergoing assisted reproduction methods or even natural conception attempts. They found that submucosal fibroids were associated with a significant decrease in implantation (RR 0.283; 95% CI 0.123–0.649), clinical pregnancy (RR 0.363; 95% CI 0.179–0.737), ongoing pregnancy/live birth rates (RR 0.318; 95% CI 0.119–0.850), and higher miscarriage rates (RR 1.678; 95% CI 1.373–2.051) [47].

2.2. Myomas and Pregnancy Outcome. The prevalence of myomas during pregnancy has been reported to be as high as 12% (range 3–12%) [57–59]. Contrary to the traditional belief that myomas tend to grow in the course of pregnancy as a result of the high inherent estrogen levels, there is currently a wealth of evidence demonstrating that their size does not significantly increase and often becomes even smaller during pregnancy [10, 60–65].

Pain is the most common symptom associated with the presence of fibroids in the pregnant woman [66]. Although pain had been initially attributed to the tentative enlargement of fibroids, subsequent studies could not confirm such a firm relationship [66]. Pain should be probably attributed to prostaglandin release from fibroid degeneration, given the efficacious analgesic effect provided by nonsteroidal anti-inflammatory drugs [60].

Fibroids during pregnancy have been linked to adverse pregnancy outcomes. In fact, an increased risk of obstetric complications, such as miscarriage, fetal malpresentation, (primarily breech), placenta previa, preterm birth, placenta abruption, postpartum hemorrhage, and cesarean section in women carrying submucosal and/or large intramural fibroids, has been reported [57, 60].

Surgical treatment of uterine myomas, irrespective of the route of the approach, results in "scarred uterus," which has been associated with increased probability of uterine rupture during subsequent pregnancy. It seems that the more the myoma nodule imbeds into the myometrium the higher the risk of uterine rupture. The risk is also increased in case of uterine perforation during hysteroscopy. Recent evidence also suggests that failure to identify and preserve fibro-neurovascular pseudocapsule during myomectomy may impair proper wound healing predisposing in uterine rupture [25–27]. In line with advice given following cesarean section, plans for future conception should be postponed, for six months after myomectomy. Nonetheless, some physicians recommend as long as a year of protected sexual intercourse following myomectomy [67]. Although, in respect to the mode of delivery in case of "scarred uterus," no clear evidence exists, the depth of the uterine wall myoma occupied should not be ignored in decision-making among normal vaginal delivery and elective cesarean section [67, 68].

2.3. Treatment of Myomas from the Fertility Aspect. In general, there is a variety of surgical and medical options for the treatment of myomas. For the past several years minimal invasive approaches such as hysteroscopy and laparoscopy have gained popularity, whereas novel alternative minimal invasive methods, such as uterine artery embolization and noninvasive techniques, such as high frequency magnetic resonance-guided focused ultrasound surgery (MRgFUS), have also been used.

Surgical intervention is mainly determined by the type and the number of myoma. Submucosal myomas are optimally treated hysteroscopically using either mechanical instruments (scissors and mechanical "cold" loops), electrocautery (thermal loops and vaporizing electrodes), laser fibers ("touch" and "nontouch" technique) [69, 70], or intrauterine morcellation [68]. Although "resectoscopic slicing" of the myoma with the use of electrical energy is the more popular and widely applied technique, it has been blamed that it can inevitably damage the surrounding healthy myometrium, mainly in type 1 or 2 according to FIGO classification myoma resection, due to the poorly defined intermyoma-myometrium cleavage plane. Therefore, from the fertility aspect, the superiority of "cold loop" myomectomy, which combines both monopolar electrocautery for the excision of the intracavitary component and mechanical blunt dissection using mechanical loop for the enucleation of the intramural component of the submucosal fibroid, has been proposed [71]. Moving the loop on the reference plane under direct visual control and minimizing inadvertent electrosurgical damage, either direct through the monopolar loop or indirect through the thermal effect, respect of the surrounding healthy myometrium is ensured. Thus, future chances of conception are enhanced and potential complications of the "scarred uterus" during pregnancy are kept to a minimum [68].

Large sessile submucosal myomas extending >50% into the myometrium may require a two-step approach. During the first step, resection of the protruding part of the myoma allows the surrounding myometrium to contract and push the remaining further into the cavity. At the later time, complete

Table 1: STEP-w classification for myomas.

Points	Size (cm)	Topography	Extension of the base	Penetration	Lateral wall
0	≤2	Low	≤1/3	0%	
1	>2–5	Middle	>1/3–2/3	≤50%	+1 point
2	>5	Upper	>2/3	>50%	

According to STEP-w classification system of myomas proposed by Lasmar and colleagues in 2005 [72, 73], the size, the topography, the extension of the base of the submucosal myoma with respect to uterine wall, and the extent of the penetration of the nodule into the myometrium are taken into account in presurgical evaluation of the viability of hysteroscopic treatment. A score of 0 to 9 is applied, assigning submucosal myomas in three groups: Group I (score 0–4): low complexity hysteroscopic myomectomy; Group II (score 5-6): complex hysteroscopic myomectomy consider preparing with GnRH-analogue and/or two-stage surgery; Group III (score 7–9): recommend alternative nonhysteroscopic treatment.

resection of the residual intramural part, which has now migrated towards the intrauterine cavity, during a second-step hysteroscopy approach is possible [31].

Given that both FIGO and ESGE classifications do not take into account the size, the topography, and the extension of the base of the submucosal myoma with respect to uterine wall, Lasmar and colleagues in 2005 proposed a presurgical classification system including these parameters along with the extent of the penetration of the nodule into the myometrium for the assessment of the viability of hysteroscopic treatment. A score of 0 to 9 is applied, assigning submucosal myomas in three groups. Group I (score 0–4) implies low complexity hysteroscopic myomectomy, and Group II (score 5-6) is suggestive of a complex hysteroscopic myomectomy and advises either preparing with GnRH-analogue or two-stage surgery, whereas Group III (score 7–9) indicates submucosal myomas, which are not suitable for the hysteroscopic approach (Table 1) [72, 73].

The use of GnRH-agonists before surgery may be beneficial in case of hysteroscopic resection of large submucosal myomas. In fact, this medication is efficient in decreasing myomas' size, endometrial thickness, and vascularization as well as minimizing distending medium intravasation and thus fluid overload [21]. Furthermore, even if intravasation occurs, GnRH-agonists may preempt sex steroid-related impact on the Na+/K+-ATPase pump, thus eliminating the effect of hyponatremic encephalopathy, the latter having been recognized as a potential fatal complication of minimal invasive uterine surgery [74]. Restoration of iron deficiency anemia with medically induced amenorrhea and scheduling operative hysteroscopy at any time instead of awaiting the follicular phase are also benefits of GnRH-agonist presurgical treatment [21, 68]. However, up to now, there is no consensus regarding the indications and the duration of treatment with GnRH-agonists prior to hysteroscopic resection. Others however argue that increased cost, medication's side effects, high recurrence rate, and the "sinking" phenomenon meaning the difficulty in operating on the myoma due to the increased distention of the endometrial cavity as a result of pharmaceutical menopause do not justify the routine use of GnRH-agonists [68]. A rational approach would be the reservation of GnRH-agonist for pretreatment only for large (>3 cm) types 1 and 2 according to FIGO classification submucosal myomas, especially when anemia due to anomalous uterine bleeding complicates their presence. In this context, selective progesterone receptor modulators (SPRMs), such as ulipristal acetate, have been proposed for preoperative treatment. SPRMs in four three-month treatment course have been also proposed for women suffering from symptomatic fibroids, who wish to preserve their fertility in the future but unwilling to get pregnant at that moment. One to three-month treatment course with SPRMS have been recommended before IVF for women carrying intramural myomas or submucosal myomas that do not significantly distort the intrauterine cavity in order to improve implantation rates [21].

Laparoscopy, open abdominal surgery and combined laparoscopy and laparotomy (laparoscopic-assisted myomectomy) are indicated for intramural and subserosal myomas [75]. Furthermore, a minority of submucosal myomas judged by Lasmar et al.'s presurgical classification system not candidates for hysteroscopic resection as well as large (>3 cm) type 2 submucosal myomas occupying the entire myometrium are better treated through laparoscopy [72, 76].

Laparoscopy is apparently preferred, when available, given the minimally invasive nature of this technique compared to the alternative operative options. In fact, shorter hospitalization and recovery period and less postoperative pain, fever, and anemia have been observed in laparoscopic compared to abdominal myomectomy [77]. In order to preserve the anatomical and functional integrity of the uterus, myomectomy should respect basic surgical principles which guide against inadvertent healthy tissue damage. As myoma pseudocapsule shares similarities with the prostate capsule, myomectomy in correspondence to prostatectomy should focus on meticulous dissection of the neurovascular bundle and avoidance of extensive electrocoagulation with high electrical power (>30 watts). Such a surgical approach that spares the pseudocapsule is described as intracapsular myomectomy and seems to be advantageous compared with the extracapsular one, in terms of blood loss, operational time, and proper hysterotomy wound healing. Keeping on this principle, postoperative deficits in uterine muscular contractility, which affect reproductive and sexual function, are minimized [23].

GnRH-agonists have been found to make myomas shrink via confluent nodular hyaline degeneration and hydropic degeneration necrosis [78]. Although these actions may benefit hysteroscopic myomectomy, they are not desirable in laparoscopic and/or abdominal myomectomy, as the cleavage plane between healthy myometrium and the pseudocapsule may be obscured, resulting in copious dissection of the

myoma and increased operating time with potential inadvertent distortion of the pseudocapsule [79].

In laparoscopy, the possibility of facing a uterine sarcoma (leiomyosarcoma followed by endometrial stromal sarcoma and carcinosarcoma) misdiagnosed as myoma exists, with a prevalence that ranges from 0.00% to 0.49% [80], although the risk has been probably overestimated [21]. To eliminate the risk of inadvertent tissue spread during surgery, "in bag" myoma excision and morcellation have been proposed to avoid ethical and medicolegal issues in case of unexpected malignancy [81–83].

Postmyomectomy adhesions, either intra-abdominal or intrauterine ones, may evolve irrespective of the surgical approach (hysteroscopy, laparoscopy, open abdominal surgery, or laparoscopically assisted myomectomy). Intrauterine synechiae are mainly linked to the hysteroscopic approach, especially when excessive electrosurgery is applied [71], unintended damage of the healthy endometrium, and myometrium proximal to the myoma occurs, and multiple submucosal myomas are resected laying on opposing uterine walls [68, 84]. Various modalities have been evaluated in the reduction of intrauterine adhesion formation following hysteroscopic myomectomy. Although hormone therapy using estrogens, application of intrauterine nonhormonal devices, urinary bladder (foley) catheters, uterine balloon, amnion graft, auto-cross-linked hyaluronic acid gel or combined hyaluronic acid, and carboxymethyl cellulose have shown promising results, none of them has been validated in abolishing posthysteroscopy intrauterine synechiae development [68, 85]. Nevertheless, early second-look hysteroscopy performed one to three weeks after surgery has been advocated to serve in prevention as well as early identification and treatment of adhesions at a stage that they will most likely be mild or moderate [86].

Intra-abdominal adhesions most often result from open abdominal surgery much more frequently as compared to laparoscopy. Poor surgical performance lacking gentle tissue handling is known to predispose to peritoneal adhesion formation. In this respect, electrocoagulation for hemostasis should be kept to a minimum. Among factors studied, 4% icodextrin solution, auto-cross-linked hyaluronic acid, expanded polytetrafluoroethylene, oxidized regenerated cellulose and the combined hyaluronic acid, and carboxymethyl cellulose have been shown to reduce postoperative adhesion development. However, there is no conclusive evidence on the relative effectiveness of these interventions [87–91].

Apart from surgical and medical strategies, the alternative minimal invasive approach of uterine artery embolization and the noninvasive high frequency magnetic resonance-guided focused ultrasound surgery (MRgFUS), which have been recently applied in myoma treatment, have not been adequately studied in cases, where fertility preservation is desired. Pregnancies have been reported following the application of both techniques, yet evidence is scanty to draw firm conclusions for women interested in childbearing [21, 37, 92, 93]. At this time fibroid artery embolization is a relative contraindication for women that desire to retain their reproductive potential [94, 95].

3. Adenomyosis and Adenomyomas

Adenomyosis is a nonneoplastic benign uterine disorder, characterized by the invasion of endometrium into the myometrium. In fact, heterotopic endometrial glands and stroma are found within the uterine musculature, surrounded by hypertropic and hyperplastic myometrium [96]. Adenomyosis typically occupies a large proportion of the uterus in a diffuse pattern rendering it bulky, and it is described as diffuse (adenomyosis). In general, posterior uterine wall is predominantly affected [97]. When adenomyosis is confined, it may present as a nodule (adenomyoma) occasionally misdiagnosed as myoma.

Adenomyosis was initially believed to be closely related to endometriosis, both having endometrial origin. In fact, it was thought that these entities represent different phenotypes of the same disorder. Later on and for the great proportion of the twentieth century, adenomyosis and endometriosis were distinguished from one another, until recently, when they were reconsidered as alternative expressions of a common entity [98]. To this end, technological advances in tissue imaging and the significant progress in molecular biology have served their best [99].

Taking into account the histologic characteristics, the extent and the location of the disease, Grimbizis and colleagues gathered diverse descriptions published in literature and proposed a new classification into diffuse and focal adenomyosis, the latter subdivided into adenomyoma with mainly solid characteristics and cystic adenomyosis, mainly described by the presence of a single adenomyotic cyst [100]. The term juvenile cystic adenomyosis (JCA) is reserved for the variant of focal cystic adenomyosis, which is present in women younger than 30 years of age with a cystic lesion larger than 1 cm and severe dysmenorrhea [101]. Polypoid adenomyomas, which present as circumscribed masses bulging into the endometrial cavity and are further subdivided into typical and atypical ones, and other forms such as adenomyomas of the endocervical type and retroperitoneal adenomyomas are considered rather distinct classes of the disease [100, 102–105].

For many years, the diagnosis of adenomyosis was based on histopathologic examination of hysterectomy specimens. Radiological modalities (hysterosalpingography) and gynecologic endoscopy procedures (hysteroscopy) for direct inspection of the intrauterine cavity did not fulfill initial expectations. Nowadays, transvaginal ultrasonography (TVS) and magnetic resonance imaging (MRI) may assist in the diagnosis of either diffuse or focal adenomyosis with a sensitivity of 72% and 77% and a specificity of 81% and 89%, respectively [106]. Still, in a significant proportion of cases only histopathology can confirm diagnosis. Given that hysterectomy is not an acceptable option for women willing to preserve their fertility, introduction of directed myometrial biopsy under sonographic, hysteroscopic, or laparoscopic guidance has yielded promising results [107–110].

While one-third of women carrying adenomyosis are asymptomatic, key clinical manifestations of this disorder include menorrhagia and dysmenorrhea. Clinical examination often reveals an enlarged tender uterus, and women may complain of chronic pelvic pain [111, 112].

The true incidence of adenomyosis is unknown, as definite diagnosis is based on histopathologic examination, whereas imaging modalities have been inconsistently used for diagnosis in the literature [99]. However, about 20% of women are believed to suffer from this entity [113].

Coexistence of adenomyosis with other gynaecological disorders, such as myomas and endometriosis, has been well established [97, 114–117]. A study evaluating the prevalence of adenomyosis using MRI scans in women diagnosed with endometriosis as compared to two control groups, one without endometriosis, defined as control group, and another without endometriosis but with a partner considered hypofertile, defined as healthy control group, confirmed the presence of adenomyotic lesions, in 79% of the endometriosis group, 28% of the control group, and 9% in the healthy control group [97]. Interestingly, the prevalence of adenomyosis reached 90% in the subset of women with endometriosis less than 36 years of age. This study contrasts findings from a previous study, in which adenomyosis diagnosed with MRI was present in only 27% of women with endometriosis [117].

3.1. Adenomyosis and Infertility. Epidemiological data suggesting that an increased prevalence of adenomyosis in multiparous women [118, 119] during the second half of their reproductive period of life should be interpreted with caution. In fact, these findings come up from older studies looking for adenomyosis on hysterectomy specimens, whereas nowadays the diagnosis of adenomyosis is feasible using noninvasive approaches, such as MRI and ultrasonography, through which the prevalence seems significant even in younger childless women. Therefore, the hypothesis that nulliparity may have a protective effect for the development of adenomyosis per se or that adenomyosis may not have a negative impact on the course of pregnancy does not seem to be fully justified.

To date there is no definite proof regarding the possible association between adenomyosis and infertility. At a first glance, the increased incidence of the disease in hysterectomy specimens of multiparous women in their 4th and 5th decade of life, presumable turns away such a link [120].

However, a pioneer study in baboons confirmed the presence of adenomyosis and reported a strong causal relation between adenomyosis and life-long primary infertility, even when cases of coexisting endometriosis were excluded (odds ratio 20.6, 95% CI 2.7–897) [121].

Subsequent reports in humans may have also suggested such a relation; however, most of them are case series with a level of evidence not strong enough to draw firm conclusions [122, 123]. Furthermore, design flaws, that is, potential coexistence of endometriosis, methodology used for diagnosis, that is, imaging instead of the traditional gold standard histopathology on hysterectomy specimen or even the less invasive targeted biopsy, may have compromised the evidence coming up from these studies. Nevertheless, the introduction of MRI during the last two decades facilitated the research on the effect of adenomyosis on reproductive outcome. In fact, the identification of the junctional zone, extending between the endometrium and the inner myometrium, and the validation of the diagnostic criteria through this imaging technique allowed the relatively accurate noninvasive diagnosis of this condition [124, 125].

It is well known that sperm following ejaculation is both actively, via progressive motility, and passively, via uterine peristaltic activity, transported in a cervicofundal direction to the ipsilateral fallopian tube, which corresponds to the ovary, where ovulation takes place [126]. Myometrial activity in the nonpregnant uterus has been shown to originate from the junctional zone, the latter being altered in the case of adenomyosis. Thus, aberrant uterine contractility impairing rapid and sustained directed sperm transport has been proposed as a plausible mechanism of infertility attributed to adenomyosis [127].

However, during the peri-implantation period, myometrial activity should be kept to a minimum to expedite apposition, adhesion, and penetration of the embryonic pole of the blastocyst into the decidualized endometrium. Research focusing on myometrial contraction patterns during embryotransfer has shown lower implantation and pregnancy rates in higher frequency junctional zone uterine activity and *vice versa* [128–130]. Although, increased contractility has been found in endometriosis, still, in adenomyosis, evidence is inadequate to definitely consider abnormal myometrial activity during the peri-implantation period as an additional mechanism for reproductive failure [99].

Endometrial receptivity seems to be also impaired in adenomyosis. Endometrial stroma vascularization has been found to be unexpectedly increased in the secretory phase, probably deranging the endometrial milieu, thus negatively affecting implantation [131].

Alterations in the expression profile of cytokines and growth factors in the endometrium have been linked to adenomyosis-associated infertility. Factors that are increased in patients with adenomyosis compared to normal fertile women include hypoxia-inducible factor 1α (HIF-1α) and interleukins (IL-6, IL-8, IL-10) as well as IL-8 receptors CXCR1 and CXCR2, matrix metalloproteinases (MMP2 and MMP9), and vascular endothelial growth factor (VEGF), whereas factors being decreased include leukemia inhibiting factor (LIF), LIF receptor α, and IL-11 [95]. A significant decrease in the expression of HOXA-10 gene during the midluteal phase has been documented in women with adenomyosis [132]. HOXA-10 gene expression is considered a necessary component of endometrial receptivity and peaks during the implantation window; therefore the decreased expression found in adenomyosis, as well as its counterpart endometriosis, may, at least partly, explain the detrimental effect of the disease in fertility [133].

Increased expression of cytochrome P450 in the endometrium along with increased aromatase activity has been proposed as possible mechanisms negatively affecting implantation in women with adenomyosis [134, 135].

In fact, local conversion of androgens to estrogens results in a hyperestrogenic endometrial environment, which sustains the increased expression of the estrogen receptor α during the secretory phase, which should have normally declined under the effect of progesterone. The hyperestrogenic endometrial milieu along with the overexpression of estrogen receptors adversely affect the expression of

cell-adhesion molecules, such as $\beta 3$ integrins, which are deemed as key elements for the development of a receptive endometrium [95].

Table 2 summarizes the mechanisms proposed for fertility impairment due to the presence of adenomyosis.

Besides the rationale for the existence of a link between adenomyosis and infertility, to date a causal relationship between these conditions has not been fully confirmed [100]. On the other hand, reports of the incidence of adenomyosis in the infertile women entering an IVF/ICSI program are inconsistent, varying from 6.9% to 34.3% [11]. A recent systematic review and meta-analysis on the effect of adenomyosis on IVF outcome reinforced the aspect of a negative impact of this condition on reproductive outcome [11]. Clinical pregnancy rates in women with adenomyosis were 28% lower as compared to controls (RR 0.72; 95% CI, 0.55–0.95). It is noteworthy that no significant difference was seen when analysis was restricted to women undergoing a single IVF/ICSI cycle (RR 0.80; 95% CI, 0.53–1.20). Interestingly, coexistence of endometriosis did not alter these results. Similarly, implantation rates were 23% lower in the adenomyosis group (RR 0.77; 95% CI, 0.63–0.93) and live birth rates were 30% lower (RR 0.70; 95% CI, 0.56–0.87). The miscarriage rate per clinical pregnancy was also significantly increased in women with adenomyosis (RR 2.12; 95% CI, 1.20–3.75). The authors concluded that screening for adenomyosis in infertile women entering an IVF program is worthy and thus should be encouraged.

3.2. Adenomyosis and Pregnancy Outcome. Data concerning the association between adenomyosis and obstetrical outcome are scanty. An early study reported a prevalence of adenomyosis of 17.2% in women undergoing cesarean hysterectomy. The authors went their thoughts a long way assuming that the presence of adenomyosis could have impair gravid uterus functionality, thereby increasing pregnancy complications, such as postpartum hemorrhage, uterine atony, and uterine rupture [136].

A subsequent and more recent study found an increased risk for preterm birth and preterm premature rupture of membranes in association with adenomyosis [137]. Among the pathogenic processes having been proposed so far, the authors pointed at decidual chorioamniotic or systemic inflammation, as the possible underlying mechanism for adenomyosis-related preterm delivery.

A review of the literature regarding obstetric complications in association to adenomyosis revealed only 29 cases. In particular, uterine rupture, postpartum hemorrhage due to uterine atony, and ectopic pregnancy were reported in relation to adenomyosis in the gravid uterus [138].

To date, evidence is not strong enough to support that adenomyosis affects the risk of obstetrical outcomes.

3.3. Treatment of Adenomyosis from the Fertility Aspect. For women suffering from adenomyosis that have completed their family, total hysterectomy could be considered the gold standard approach for symptom relief. However, for a patient, who has a desire to preserve her reproductive function, various uterine-sparing surgical techniques have been proposed. For patients with focal disease and for selected cases of more diffuse adenomyosis, excision of the adenomyoma or cystectomy for cystic focal adenomyosis has been proposed [100]. Partial removal of the abnormal tissue or cytoreductive surgery is reserved for cases of diffuse adenomyosis with special attention to preserve a functional uterus [100]. Nonexcisional invasive treatments include laparoscopic (electrocoagulation, uterine artery ligation), hysteroscopic (ablation, transcervical resection), and other treatments, the latter including uterine artery embolization [139] and ablation with MRI-guided focused ultrasound surgery (MRIgFUS), thermoballoon, radiofrequency, or microwave [100].

Conservative medical approaches have also been applied to relieve symptoms and in women wishing to get pregnant. GnRH-analogues, aromatase inhibitors, the levonorgestrel-releasing intrauterine contraception device, a danazol intrauterine contraception device, and the continuous use of estrogen-progestin oral contraceptives are all included in available treatment options [113, 140–146].

4. Conclusions

Myomas and adenomyosis represent common benign uterine pathologies with a remarkable prevalence in women of reproductive age. Although these entities often coexist, their pathophysiology and clinical characteristics are distinct. However, both disorders have been repeatedly linked to infertility.

In the era of evidence based medicine, submucosal myomas, which by definition distort the intrauterine cavity, have been consistently linked to an adverse effect on reproductive outcome and should be removed. The evidence is also abundant for subserosal myomas, which do not seem to be associated with infertility and adverse pregnancy outcome. However, the impact of intramural myomas on reproduction potential is not clear enough. Contemporary evidence suggests a causal relationship between intramural myomas larger than 4 cm in diameter and infertility.

The presence of submucosal and/or large intramural myomas has also been linked to adverse pregnancy outcomes, such as increased risk for miscarriage, fetal malpresentation, placenta previa, preterm birth, placenta abruption, postpartum hemorrhage, and cesarean section.

In respect to adenomyosis, the utilization of magnetic resonance imaging and modern ultrasonography has provided adequate accuracy in the diagnosis of the disease abolishing the need for histopathologic confirmation. Despite the confirmed clinical association between adenomyosis and infertility, to date a causal relationship between these conditions has not been fully confirmed, although it has been repeatedly suggested. An association between obstetrical complications, such as preterm birth, preterm premature rupture of membranes, uterine rupture, postpartum hemorrhage, and ectopic pregnancy adenomyosis, has also been reported. Still, the precise role of adenomyosis on reproductive outcome is not well clarified.

Table 2: Mechanisms proposed for fertility impairment on the presence of myomas and adenomyosis.

	Mechanism
Myomas	(i) Distortion of the uterine cavity rendering the endometrial contour anomalous may compromise implantation potential (ii) An enlarged and deformed fibroid uterus may hamper sperm transport (iii) Cervical displacement may hinder sperm passage into the cervical canal (iv) Altered myometrial contractility may compromise sperm progression into the female reproductive system (v) Alteration to the endometrial and myometrial blood supply may interfere with both uterine contractility and implantation (vi) Retained menstrual efflux due to a deformity of the uterine cavity may interfere with both sperm transport and implantation (vii) Deviation or obstruction of the tubal ostia may compromise tubal patency (viii) Alteration of the tubo-ovarian anatomic relation may impede ovum collection from the fimbrial end following ovulation (ix) Chronic endometrial inflammation due to myomas lying adjacent to the endometrium may alter endometrial milieu (x) Histologic alterations attributed to myomas lying close or in contact to the endometrial surface may impair implantation (xi) Among molecular markers of endometrial receptivity, a decrease in HOX gene expression throughout the endometrium and not simply over a submucosal myoma may suggest that impairment of fertility may be attributed to a global effect and not simply a focal change over the myoma
Adenomyosis	(i) Aberrant uterine contractility, originating from the junctional zone, which is broadened in case of adenomyosis, may impair rapid and sustained directed sperm transport (ii) Abnormal myometrial activity during the peri-implantation period may hinder apposition, adhesion, and penetration of the embryonic pole of the blastocyst into the decidualized endometrium (iii) Increased endometrial stroma vascularization in the secretory phase may derange the endometrial milieu, thus negatively affecting implantation (iv) Alteration in the expression profile of cytokines and growth factors in the endometrium, such as increased expression of hypoxia-inducible factor 1α (HIF-1α) and interleukins (IL-6, IL-8, IL-10) as well as IL-8 receptors CXCR1 and CXCR2, matrix metalloproteinases (MMP2 and MMP9) and vascular endothelial growth factor (VEGF) and decreased expression of leukemia inhibiting factor (LIF), LIF receptor α, and IL-11 may be linked to adenomyosis-associated infertility (v) Decreased expression of HOXA-10 gene during the midluteal phase, which is considered a necessary component of endometrial receptivity and peaks during the implantation window, may negatively affect implantation (vi) Hyperestrogenic endometrial environment due to the increased expression of cytochrome P450 along with increased aromatase activity in the endometrium sustains the increased expression of the estrogen receptor α during the secretory phase. This in turn adversely affects cell-adhesion molecule expression, such as β3 integrins, which are deemed as key elements for the development of a receptive endometrium

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Research Article

Expression Pattern of G-Protein-Coupled Estrogen Receptor in Myometrium of Uteri with and without Adenomyosis

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Objective. To compare the expression of G-protein-coupled estrogen receptor (GPER) in the junctional zone and outer myometrium of the proliferative and secretory phases of women with and without adenomyosis. *Methods.* A total of 76 women were included in this study, 42 with adenomyosis (proliferative phase, $n = 23$; secretory phases, $n = 19$) and 34 controls (proliferative phase, $n = 16$; secretory phases, $n = 18$). Protein and total RNA were extracted from the junctional zone (JZ) and outer myometrium (OM). GPER protein and mRNA expression levels were evaluated by the use of western blotting and real-time quantitative polymerase chain reaction (RT-qPCR). *Results.* The expression of GPER protein and mRNA in women with adenomyosis was significantly higher than that of control subjects, both in the junctional zone and in the outer myometrium and both in the proliferative and in the secretory phases. *Conclusion.* The significant and consistent increase in GPER expression in adenomyosis compared with control subjects, regardless of whether it was in the proliferative or secretory phases and regardless of whether it was in the JZ or OM, suggests that GPER plays an important role in the pathogenesis of the adenomyosis.

1. Introduction

Adenomyosis is characterized by the extension of endometrium into the myometrium, along with myometrial smooth muscle cells hyperplasia and hypertrophy. It is common in women of reproductive age and often regresses after menopause [1, 2]. Estrogen plays a crucial role in the pathogenesis of adenomyosis. The effects of estrogen are mediated by two types of estrogen receptors: nuclear estrogen receptors (ER-α and ER-β), which are members of the nuclear receptor family of intracellular receptors, and membrane estrogen receptor (GPER or G-protein-coupled estrogen receptor) [3]. Adenomyosis is known to be associated with changes in the expression of ER-α and ER-β. A recent study showed that ER-α expression was reduced in the mid-secretory phase endometrium of women with adenomyosis, whereas ER-β was increased not only in the endometrium but also in the inner myometrium and outer myometrium of women with adenomyosis compared with control subjects [4]. However, the expression of GPER in the uterus of women with adenomyosis has not been previously investigated. In this study, we studied the expression of GPER in the outer and inner myometrium (junctional zone) of women with adenomyosis and compared the results to a group of control subjects.

2. Materials and Methods

2.1. Subjects. All subjects recruited in this study were premenopausal women who underwent hysterectomy at the Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China.

The inclusion criteria included the following:

(1) Regular 25–35 days' cycles

(2) No hormonal treatment or having not used an intrauterine device for 3 months prior to hysterectomy

(3) No evidence of leiomyoma.

There were 2 groups of women recruited. Group I consisted of 42 women with adenomyosis, histologically confirmed. In this study, the diagnosis of adenomyosis was based on histological confirmation of the presence of endometrial tissue more than 2.5 mm below the endomyometrial junction or a JZ thickness of more than 12 mm [5]. The additional inclusion criterion for women in this group was the presence of dysmenorrhea with or without menorrhagia prior to the surgery. In this respect, we have included only subjects with symptomatic adenomyosis, which was the underlying reason for their request for hysterectomy. Group II consisted of 34 subjects with no evidence of adenomyosis who underwent hysterectomy due to early cervical cancer or ovarian cancer. The exclusion criteria for this group of women were preoperative radiotherapy or chemotherapy and involvement of the endometrium or myometrium by neoplasm. As the study was based on histological confirmation of adenomyosis on hysterectomy specimens and the collection of biopsy from different parts of the excised uterine specimen, it was necessary to recruit control subjects who required hysterectomy for a different clinical reason. However, it was also considered necessary to exclude uterus with significant myometrial pathology such as myoma which could have altered histological findings in the junctional zone or myometrium. Given that it was unusual for women of reproductive age to have a normal uterus removed other than those who suffered from early cervical or ovarian cancer, we have chosen to include this group of women as control subjects. As it happened, all subjects included in the study belonged to early cervical cancer.

Excisional biopsy of the junctional zone and outer 1/3 of the myometrium was performed from the anterior fundal wall of each hysterectomy specimen. The biopsy of the outer 1/3 myometrium was undertaken from 2 mm beneath the serosal surface of the uterus, whereas the biopsy from the junctional zone was undertaken 2-3 mm beneath the endometrium, taking special care not to include any normal endometrial tissue in the biopsy.

2.2. Histological Dating. Histological dating of the endometrium from the uterine specimens was performed by an experienced pathologist with the use of standard criteria [6]. The specimens were then classified into proliferative (PP) or secretory phases (SP).

2.3. Western Blotting. Homogenized tissues were lysed for protein extractions. Protein extracts (30–50 mg) were separated by electrophoresis on 12% sodium dodecyl sulfate-polyacrylamide gels. Proteins were transferred to polyvinylidene fluoride (PVDF) membranes; incubated with rabbit anti-GPER (ab39742; from Abcam, Cambridge, Massachusetts) as a primary antibody; and then developed with a secondary anti-rabbit antibody (obtained from Cell Signaling Technology, Danvers, Massachusetts). The signal was detected using a LI-COR Biosciences Odyssey Infrared Imaging System (LI-COR, Lincoln, Nebraska). Equivalent protein loading and transfer efficiency were verified by staining for GAPDH (D16H11, from Cell Signaling Technology, Danvers, Massachusetts).

Table 1: Primer sequences for GPER.

	Primer	Sequence
GPER	Forward	5′-TGACCATCCCCGACCTGTAC-3′
	Reverse	5′-CAGGTGAGGAAGAAGACGCT-3′
GAPDH	Forward	5′-CTCCTCCACCTTTGACGCTG- 3′
	Reverse	5′-TCCTCTTGTGCTCTTGCTGG-3′

2.4. Quantitative Real-Time Polymerase Chain Reaction. Total RNA was extracted and purified from the tissue specimens. 1.0 μg RNA was reverse transcribed with random primers using Superscript II reverse transcriptase (Life Technologies, Inc., Melbourne, Australia). Quantitative PCR was performed in the presence of SYBR Green (Tiangen Biotech, China), and amplicon yield was monitored during cycling in an ABI 7500 Real-Time Polymerase Chain Reaction System (Applied Biosystems, Grand Island, New York) that continually measured fluorescence caused by the binding of the dye to double-stranded DNA. The cycling conditions were 95°C for 15 minutes, 40 cycles at 95°C for 10 seconds, and 60°C for 32 seconds. The cycle at which the fluorescence reached a set threshold (cycle threshold) was used for quantitative analyses. The cycle threshold in each assay was set at a level at which the exponential increase in amplicon abundance was approximately parallel between all samples. Relative gene expression was calculated in relation to an internal control for normalization (glyceraldehyde 3-phosphate dehydrogenase, GAPDH), using the comparative cycle threshold method. Primer sequences for GPER and GAPDH are presented in Table 1.

2.5. Ethics. This study was approved by Ethical Committee of Clinical Research of Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China. Written informed consent was obtained from all patients who participated in this study. This study was conducted in accordance with the Declaration of Helsinki (1964).

2.6. Statistical Analysis. Normally distributed data were presented as mean ± standard deviation. Student t-test was used to test for differences between groups. Statistical analyses were performed with the use of SPSS 19.0 for Windows. For all tests, a p value of <0.05 was considered statistically significant.

3. Results

3.1. Demographics. A total of 42 women with adenomyosis and 34 women without adenomyosis (control subjects) were included in the study. In group I, 23 specimens were classified as proliferative and 19 as secretory. In group II, 16 specimens were classified as proliferative and the remaining 18 as secretory. The demographic details of these two groups of women are compared in Table 2. There was no significant difference in any of the features between the two groups.

Using western blotting, GPER protein expression signals appeared at approximately 42 kd (Figure 1). The position of

Table 2: Demographic details of patients with adenomyosis and control subjects.

	Adenomyosis	Control	p value
Age (years)	44.1 ± 2.9	43.0 ± 4.4	0.07
Parity	1.3 ± 0.1	1.4 ± 0.1	0.45
Miscarriage	2.1 ± 1.4	1.8 ± 1.1	0.06
Body mass index, kg/m^2	23.2 ± 2.7	24.1 ± 3.3	0.09

Values are given in mean ± standard deviation.

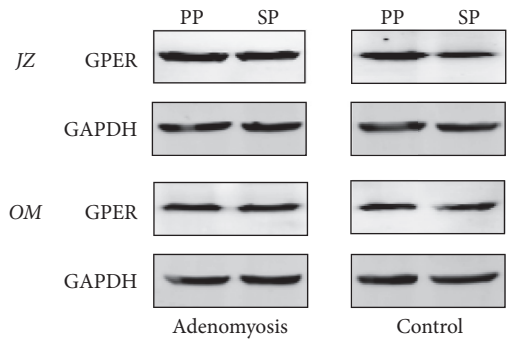

Figure 1: Representative western blotting of G-protein-coupled estrogen receptor (GPER) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in biopsy specimens from the junctional zone (JZ) and outer myometrium (OM) in the proliferative phase (PP) and secretory phase (SP).

the GPER signal was the same as that observed in MCF-7 breast cancer cells (data not shown).

3.2. Comparison of GPER Expression between Proliferative Phase and Secretory Phase. In Table 3, the GPER protein and mRNA expression in the proliferative and secretory phase were compared, separately in women with and without adenomyosis, and in the JZ and OM.

In the control subjects, the expressions of both protein and mRNA in the JZ in the proliferative phase were both significantly ($p < 0.05$) higher than those of the secretory phase, whereas the expressions of both protein and mRNA in the OM in the proliferative phase and the secretory phase were similar.

In women with adenomyosis, in contrast, there was no significant difference in the expression of GPER protein and mRNA level between the proliferative phase and secretory phase in both the JZ and OM.

3.3. Comparison of GPER Expression between Junctional Zone and Outer Myometrium. In Table 3, the GPER protein and mRNA expression in the junctional zone and outer myometrium were compared, separately in women with and without adenomyosis and in the proliferative and secretory phases.

In the control group, in the proliferative phase, the expression of both protein and mRNA in the JZ was higher than that of the OM. In the secretory phase, however, the expression of both protein and mRNA in the JZ was similar to that of the OM.

In women with adenomyosis, on the other hand, the expression of both protein and mRNA in the JZ were higher than that of the OM in both the proliferative and secretory phases.

3.4. Comparison of GPER Expression between Adenomyosis and Control Groups. In Table 3, the GPER protein and mRNA expression in women with and without adenomyosis were compared, separately in the junctional zone and outer myometrium and in the proliferative and secretory phase.

In the JZ, the GPER protein expression and the mRNA level in women with adenomyosis were significantly higher than that of control subjects in both the proliferative phase and secretory phase.

In the OM, the GPER protein expression and the mRNA level in women with adenomyosis were also significantly higher than that of control subjects in both the proliferative phase and secretory phase.

4. Discussion

In this study, we found that the expression of GPER protein and mRNA in women with adenomyosis was significantly higher than that of women without adenomyosis, both in the junctional zone and in the outer myometrium and both in the proliferative and in the secretory phases.

Adenomyosis is often considered to be an estrogen-dependent disease with changes in structure and function of the JZ [1] observed in the majority of cases. The JZ is responsible for uterine peristalsis which regulates sperm transport and implantation [7, 8]. Structural changes in the JZ in adenomyosis commonly include JZ hyperplasia and thickening [9]. Ultrastructurally, the myocytes in the JZ of uterus affected by adenomyosis appeared smaller [10]. Abnormal expression of oxytocin receptor in the JZ of women with adenomyosis has been observed [11], which may explain the occurrence of hyperperistalsis and dysperistalsis, in turn leading to dysmenorrhea and disturbance of reproductive function. However, the outer myometrium, whose primary function is involved with parturition [12], is often not affected in adenomyosis until a later stage.

There are two different types of estrogen receptors. The nuclear estrogen receptors (ER-α and ER-β) mediate gene expression through binding to estrogen receptor elements in the promotor and regulatory regions of the target genes; in contrast, GPER, the other type of estrogen receptor, mediates rapid cellular effects. GPER is a membrane estrogen receptor, a 7-transmembrane spanning G-protein-coupled receptor, also called G-protein-coupled receptor 30 (GPR30) [13]. GPER is structurally and genetically unrelated to ER-α and ER-β and expressed independently [3]. It binds to estrogen with high affinity, whereas binding affinities of GPER for other steroid hormones are very low [14]. In earlier studies, estrogen effects can be mimicked by selective GPER agonist or antagonist, whereas, in GPER knockout mice, these effects are absent or reduced, suggesting that GPER plays an essential role [15]. Expression of GPER has been described in multiple physiological systems and tissues, including the breast, heart, endothelium, brain, bone, adrenal, kidney,

Table 3: Relative GPER protein and mRNA expression levels (GPER/GAPDH).

	Adenomyosis group ($n = 42$)		Control group ($n = 34$)	
	JZ	OM	JZ	OM
Relative GPER protein expression levels				
PP	$1.12 \pm 0.072^{b,c,e}$ ($n = 23$)	$0.96 \pm 0.043^{b,c,e}$ ($n = 23$)	$0.95 \pm 0.027^{a,c,e}$ ($n = 16$)	$0.83 \pm 0.051^{b,c,e}$ ($n = 16$)
SP	$1.09 \pm 0.076^{b,c,e}$ ($n = 19$)	$0.94 \pm 0.052^{b,c,e}$ ($n = 19$)	$0.82 \pm 0.097^{a,d,e}$ ($n = 18$)	$0.84 \pm 0.086^{b,d,e}$ ($n = 18$)
Relative GPER mRNA expression levels				
PP	$1.52 \pm 0.12^{b,c,e}$ ($n = 23$)	$1.31 \pm 0.09^{b,c,e}$ ($n = 23$)	$1.28 \pm 0.07^{a,c,e}$ ($n = 16$)	$1.04 \pm 0.1^{b,c,e}$ ($n = 16$)
SP	$1.51 \pm 0.14^{b,c,e}$ ($n = 19$)	$1.29 \pm 0.18^{b,c,e}$ ($n = 19$)	$1.09 \pm 0.13^{a,d,e}$ ($n = 18$)	$1^{b,d,e}$ ($n = 18$)

Values expressed as mean ± standard deviation. [a]Comparison between proliferative phase and secretary phase (same group and zone), $p < 0.05$, Student t-test; [b]comparison between proliferative phase and secretary phase (same group and zone), $p \geq 0.05$, Student t-test; [c]comparison between outer myometrial zone and junctional zone (same group and phase) $p < 0.05$, Student t-test; [d]comparison between outer myometrial zone and junctional zone (same group and phase) $p \geq 0.05$, Student t-test; [e]comparison between adenomyosis and control group (corresponding phase and zone) $p < 0.05$, Student t-test.

endometrium, and ovary [15–20]. The changes in GPER expression in a number of gynecological conditions such as the endometrium of women with endometriosis [21] and smooth muscle of myoma [22] have been examined. On the other hand, whilst the expressions of nuclear estrogen receptors (ER-α and ER-β) have been examined in the inner and outer myometrium of adenomyosis [12], the expression of GPER in adenomyosis has not previously been studied. Evidence has shown that GPER agonist G1 can lead to apoptosis in endometriosis and suppress proliferation of endometriotic stromal cells [23]. GPER is closely related to the outcome of estrogen therapy on various estrogen-dependent diseases [24–26] and selective GPER ligands (such as GPER agonist G1 and antagonist G15) have been shown to exert control of these diseases [27–29]. A better understanding of the role played by GPER in the pathogenesis of adenomyosis may open up opportunity for GPER-targeted therapy for the condition [15].

The special design of this study enabled us to examine the cyclical change and anatomical variation of GPER expression in control subjects, in addition to comparing GPER expression between women with and without adenomyosis. One possible limitation of our study was that biopsy specimens from the junctional zone of women with adenomyosis often contained foci of endometrial tissue which could have contributed to the observed difference in results between the two groups of subjects.

Cyclical Changes. In our study, in control subjects, we observed that the expression of GPER in the proliferative phase in the JZ was higher than that of secretory phase of the JZ; however the cyclical change was not observed in the OM. In women with adenomyosis, the cyclical change appeared to have disappeared. Similar cyclical changes in the ultrastructure of myocytes in the JZ and OM were observed in our previous study [10].

Anatomical Variation. As for the anatomical variation, in control subjects, the expression of GPER in the JZ was higher than that of the OM in the proliferative phase but not the secretory phases. In contrast, in women with adenomyosis, the expression of GPER in the JZ was higher than that of the OM in both the proliferative phase and the secretory phases. In other words, the anatomical variation between the JZ and OM in women with adenomyosis was consistently observed, independent of the phases of the cycle.

Adenomyosis versus Control. In contrast to the observations relating to the cyclical and anatomical variation of GPER in which significant difference in control subjects was found only in the proliferative phase and JZ, there was consistent and significant difference in GPER expression regardless of the stage of the cycle (proliferative or secretory) or anatomy (JZ or OM).

Taken together, the cyclical and anatomical variation of GPER observed in control subjects in this study is consistent with our current understanding that the effects of estrogen are more dominant in the proliferative phase than the secretory phase, and more pronounced in the JZ than in the OM. In addition, the special design of our study enabled us to control for two important confounding variables (cyclical changes and anatomical variation); by doing so, the variance in results due to the effect of these confounding variables was reduced. Whilst it is already known that the expressions of estrogen nuclear receptors ER-β (but not ER-α) and progesterone receptor are different between women with and without adenomyosis [4], the additional finding in this study that GPER expression is also altered in women with adenomyosis confirms the notion that adenomyosis is associated with alteration in several different steroid receptors.

Overall, the finding observed in this study appears to have provided a molecular basis for the smooth muscle hyperplasia and hypertrophy observed in adenomyosis [1, 2]. Specifically, it seems plausible that the abnormally elevated GPER expression in the JZ is one mechanism by which the smooth muscle cells continue to proliferate in adenomyosis.

To conclude, we have found significant and consistent increase in GPER expression in adenomyosis, in both

proliferative and secretory phases and in both the JZ and OM, suggesting that GPER plays an important role in the pathogenesis of the condition. It remains to be seen if treatment targeting the expression of GPER by the use of selective GPER ligands may help to treat or prevent the condition.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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Research Article

Sonographic Signs of Adenomyosis Are Prevalent in Women Undergoing Surgery for Endometriosis and May Suggest a Higher Risk of Infertility

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Objectives. To determine the prevalence of ultrasound features suggestive of adenomyosis in women undergoing surgery for endometriosis compared with a control group of healthy women without endometriosis. *Methods*. Retrospective case-control study comparing women with intractable pain or infertility, who underwent transvaginal ultrasound and subsequent laparoscopic surgery, with a control group of healthy women without a previous history of endometriosis. A diagnosis of adenomyosis on TVUS was made based on asymmetrical myometrial thickening, linear striations, myometrial cysts, hyperechoic islands, irregular endometrial-myometrial junction, parallel shadowing, and localized adenomyomas and analyzed for one sign and for three or more signs. *Results*. The study and control groups included 94 and 60 women, respectively. In the study group, women were younger and had more dysmenorrhea and infertility symptoms. The presence of any sonographic feature of adenomyosis, as well as three or more signs, was found to be more prevalent in the study group, which persisted after controlling for age, for all features but linear striations. Women in the study group who had five or more sonographic features of adenomyosis had more than a threefold risk of suffering from infertility (OR = 3.19, $p = 0.015$, 95% CI; 1.25–8.17). There was no association with disease severity at surgery. *Conclusions*. Sonographic features of adenomyosis are more prevalent in women undergoing surgery for endometriosis compared to healthy controls. Women with more than five features had an increased risk of infertility.

1. Introduction

Adenomyosis is a benign disorder of the uterus that is defined as the presence of endometrial glands and stroma within the uterine myometrium. Reports of the prevalence of adenomyosis are highly heterogenous and inconsistent and are dependent on the population studied and the methodology used for evaluation. Many studies rely on histological findings in women undergoing hysterectomies and report a higher prevalence, as hysterectomies are performed on women with a known indication [1–4]. Adenomyosis is most often found in women between 40 and 50 years of age [1]. This age range may be explained by the more common performance of hysterectomies in this age group, but may also be attributed to prolonged life-time exposure to hormones [5]. The most commonly reported associated symptoms are abnormal uterine bleeding and dysmenorrhea that occur in approximately 65% of patients [5]. Adenomyosis often coexists with deep endometriosis. The association between adenomyosis, endometriosis, and infertility is still under debate and the mechanism is poorly understood. Patients with coexisting deep infiltrating endometriosis and uterine adenomyosis may constitute a subgroup with a particularly poor reproductive prognosis [6–10]. A recent meta-analysis described a 68% reduction in the likelihood of pregnancy in women seeking conception after surgery for rectovaginal and colorectal endometriosis [11].

The improved resolution of transvaginal ultrasound (TVUS) probes enables a detailed and thorough assessment of the uterine structure with detection of features, which

have not been previously seen. Recent studies report the prevalence of adenomyosis based on the imaging method that was used, such as TVUS [12–14] or magnetic resonance imaging (MRI) [15–17]. Adenomyosis may be reliably detected by both TVUS and MRI without the need for histological examination of a biopsy specimen [15, 18]. The advantages of TVUS over MRI are its wide availability and economy. Recent studies advocate that TVUS be used as the first line imaging modality in women undergoing preoperative evaluation before endometriosis surgery, for determining the extent and severity of the disease, and mapping the way for the surgeon [19–21]. TVUS is considered an accurate diagnostic tool for the diagnosis of adenomyosis, and can therefore be used as standard clinical practice for the noninvasive diagnosis of adenomyosis [12, 18, 22–24]. The most commonly described two dimensional (2D) TVUS findings for adenomyosis are a heterogenous myometrium, abnormal myometrial echo texture, myometrial cysts, a globular and/or asymmetric uterus, ill-defined margins between the endometrium and the myometrium, echogenic linear striations, and focal adenomyomas [12–14, 25]. Three-dimensional (3D) TVUS also allows clear visualization of the endometrial-myometrial junctional (EMJ) zone and enables early diagnosis of adenomyosis [26, 27].

While the prevalence of adenomyosis in women undergoing surgery has been described, there is less data on the association with endometriosis and on the prevalence in asymptomatic women. The aim of our study was to determine the prevalence of ultrasound features suggestive of adenomyosis in women undergoing laparoscopic surgery for endometriosis in a tertiary referral center compared with a control group of healthy women without endometriosis attending a medical screening facility, using 2D and 3D TVUS. Our secondary aim was to explore the relationship between these sonographic features with demographic parameters and symptoms, particularly infertility.

2. Patients and Methods

2.1. Patients and Setting. We retrospectively studied women who were referred to our endometriosis center between November 2011 and March 2013 and underwent a dedicated TVUS and subsequent laparoscopic surgery. Out of the 250 patients who were examined during the study period, 94 underwent surgery at our institution and were included in the analysis. The indication for surgery was either intractable pain not responsive to conservative management or persistent infertility. The remaining women either did not qualify for surgery, preferred conservative treatment, or were operated on at another institution and therefore were not included in the analysis. The patients' demographic information, clinical history, and symptoms were obtained from the electronic hospital records and from outpatient referral documents and included: age, body mass index (BMI), parity, previous cesarean sections, previous surgery for endometriosis, smoking history, dysmenorrhea, dyspareunia, urinary and gastrointestinal symptoms, infertility history, previous fertility treatment and type, and number of previous in vitro fertilization (IVF) cycles. The control group consisted of reproductive age women attending a general medical screening facility in our institution, who underwent a TVUS as part of the annual checkup, on the days that the expert sonographer performed the clinical round. Women were included at random without preselection. Most of the women attending the medical screening facility were past their reproductive period, so it was difficult to find eligible patients. Women with a previous history of endometriosis, previous surgery for endometriosis or following a hysterectomy, were excluded from the control group analysis.

Ethical approval was obtained from our local research ethics committee (IRB). Written informed consent was not required as the ultrasound assessment was offered as part of standard clinical care at our center and in the medical screening facility. No procedure was performed for the purpose of the study and no identifying information is included in the data presented here.

2.2. Evaluation of Adenomyosis and Endometriosis. A TVUS scan was carried out using a 7.5 MHz probe with 2D/3D capabilities (Voluson 730 and E6, and P6, GE Medical Systems, Villach, Austria), in a standardized way by the same imaging expert. The examination included a thorough evaluation of all pelvic viscera and was performed at any time of the menstrual cycle regardless of hormonal therapy. Bowel preparation was not utilized. The uterus was studied in a midsagittal plane identifying the uterine cavity and cervical canal, moving to the right and left in order to cover the entire uterine cavity. The probe was then rotated 90 degrees to the left to view the uterus in the transverse plane. The myometrium was thoroughly evaluated for any abnormalities in all planes. The analysis for both groups was based on stored 2D images and cine loops. All women were examined by the same expert sonographer using the same methodology. We did have 3D capabilities available for the study group but decided not to use them for the sake of equal comparison using the same modalities for both groups.

A diagnosis of adenomyosis was made at the time of the exam, when any one of the following features was present: asymmetrical myometrial thickening (in the absence of fibroids), parallel shadowing, myometrial cysts, hyperechoic islands, irregular endometrial-myometrial junction (EMJ), linear striations, and localized adenomyomas (Figures 1–4). An adenomyoma was defined as a nodular, heterogeneous myometrial mass with ill-defined borders [23]. These features were chosen because they are all recognized as reliable morphological sonographic markers for adenomyosis [12–14] and can be differentially diagnosed from fibroids [23, 28]. The accuracy of these findings was evaluated against the pathological report when available. In order to increase accuracy, we looked at a combination of features and calculated the same parameters for three or above and for five or above sonographic features.

A diagnosis of endometriosis on ultrasound was based on the presence of ovarian endometriomas, deeply infiltrative endometriotic nodules, signs of pelvic adhesions (kissing ovaries or absent sliding of viscera), or overt tubal disease [19–21, 27]. The severity of endometriosis at surgery was evaluated based on the Revised American Society for Reproductive

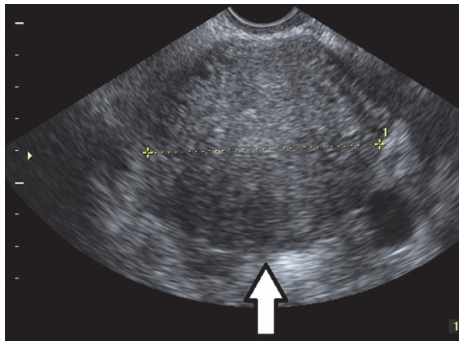

Figure 1: Parallel shadowing. 2D image in transverse view of a uterus with parallel hypoechoic lines through the myometrium (arrow).

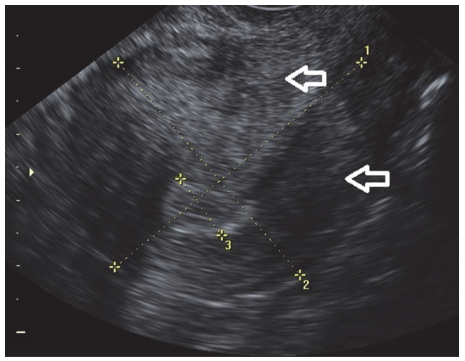

Figure 2: Asymmetrical myometrial thickening. 2D longitudinal view of a uterus with asymmetrical distances from the endometrium to the anterior and posterior serosal surfaces (arrows).

Medicine (ASRM) Classification [29], and the histopathological reports were reviewed. We included only the women for whom we had histological confirmation of endometriosis.

2.3. Statistical Analysis. Statistical analysis was performed using SPSS software version 20 (SPSS Inc., IBM corporation, Chicago, IL, USA). Continuous variables were expressed as means ± SD or medians, while categorical variables were expressed as percentages. The Fisher exact test was used to detect differences in percentages and the Student t-test was used to compare means. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for the diagnosis of adenomyosis on ultrasound. Associations between various demographic, symptomatic and clinical variables and disease severity at surgery, and the presence of adenomyosis on ultrasound were assessed using logistic regression, and univariate and multivariate analyses were performed. The analysis was performed for at least one sign, three signs or more, and five or above signs. The associations between sonographic features of adenomyosis and demographic variables were assessed using logistic regression for 3 models: without adjustment for variables, with adjustment for age, and with adjustment for age, smoking, BMI, and previous cesarean sections. Statistical significance was set at $p < 0.05$.

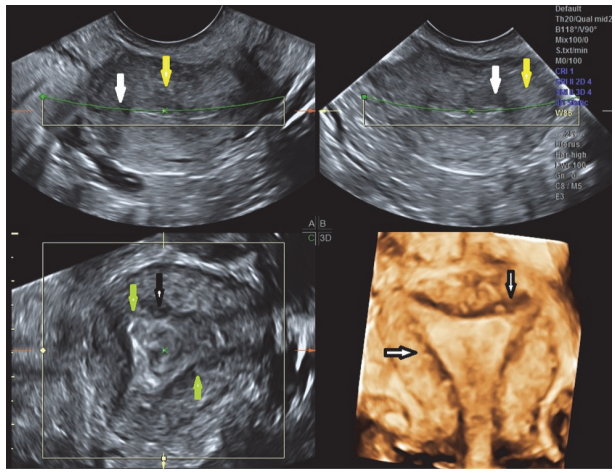

Figure 3: Severe adenomyosis with multiple sonographic signs: multiplanar and 3D rendering of an anteverted uterus with multiple sonographic signs: myometrial cysts (white arrow), hyperechoic islands (yellow arrow), linear striations (green arrow), and irregular EMJ (black arrow).

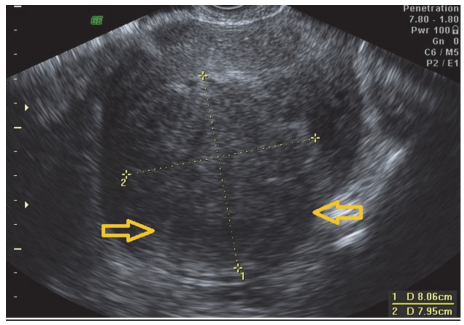

Figure 4: Localized adenomyoma. 2D image of an anteverted uterus with a localized adenomyoma in the posterior fundal wall (between yellow arrows).

3. Results

3.1. Demographic and Clinical Characteristics. Ninety-four women were included in the study group, all of which underwent TVUS and subsequent laparoscopic surgery over the study period, and sixty women in the control group. Demographic data and patient symptoms are presented in Table 1. None of the women were menopausal. In the study group symptoms and complaints included dysmenorrhea (92.5%), dyspareunia (64.1%), urinary complaints (28.6%), gastrointestinal complaints (53.8%), and infertility (37.2%). All patients described long-standing symptoms before being referred to our center. Of the 94 women, 49 (52%) had undergone previous surgery for endometriosis. Twenty-five women (26.6%) had undergone IVF treatments prior to surgery, the median number of IVF treatments was 5 (range 1–16), with 17 women undergoing 3 cycles or more, without success. The indication for infertility treatment in all of these women was female infertility, and there were no cases of male factor infertility.

Table 1: Demographic data and symptoms in women undergoing surgery for endometriosis versus the control group.

	Endometriosis ($N = 94$)	Control ($N = 60$)	p
Age, mean ± SD, years	34.1 ± 6.0	42.7 ± 3.2	<0.001*
BMI, mean ± SD, kg/m^2	23.6 ± 4.8	23.8 ± 4.1	0.830
Parous (%)	42 (44.7%)	58 (96.7%)	<0.001*
Parity, mean ± SD	0.9 ± 1.2	2.4 ± 0.9	<0.001*
Previous cesarean section (%)	0.2 ± 0.6	0.3 ± 0.7	0.183
Smoker (%)	28 (29.8)	9 (15.0)	0.052
Previous laparoscopy (%)	47 (50.0)	2 (3.3)	<0.001*
Dysmenorrhea (%)	86 (92.5)	14 (25.0)	<0.001*
Infertility (%)	32 (35.6)	14 (23.3)	0.148
Previous IVF treatment (%)	25 (30%)	9 (15%)	0.038*
Number of IVF cycles, mean ± SD	1.8 ± 3.9	0.6 ± 2.2	0.022*

SD: standard deviation; IVF: in vitro fertilization treatment. *Statistically significant finding.

In the control group (see Table 1), women were older and more parous with a higher mean parity. None of the women were menopausal. Two women had undergone previous laparoscopy for indications other than endometriosis. There was less infertility and less need for IVF treatments, and only four women had undergone three IVF cycles or more.

3.2. Surgeries. All of the patients underwent laparoscopic surgery by a multidisciplinary team of trained endoscopic surgeons, which included urological and colorectal surgeons as required. The indication for surgery was intractable pain not amenable to conservative treatment or infertility. Adenomyosis or the concurrent presence of fibroids were not sole indications but could be complementary and thus did not affect surgical indication in itself. Fifty-seven (60.6%) of the women had endometriomas, 11 (11.7%) bladder nodules, 39 (41.5%) vaginal nodules, 48 (51.1%) pouch of Douglas obliteration, 20 (21.3%) bowel nodules (rectum, bowel, and pouch of Douglas), and 50 (53.2%) uterosacral ligament involvement. The mean disease severity (ASRM) score at surgery was 51.28 ± 38.25 (range 1–148), and the median ASRM stage was 4 (range 1–4). Fifteen (16%) patients had stage I, 4 (4.3%) stage II, 19 (20.2%) stage III, and 56 (59.6%) stage IV disease. Women with stage I or II disease also underwent surgery for intractable pain unresponsive to conservative management or infertility. Hysterectomies were performed only in 14 women who suffered from severe symptomatic adenomyosis and endometriosis who had completed family planning. Thus, histological confirmation of adenomyosis in hysterectomy specimens was available only in these women (15%), providing a sensitivity of 100%, specificity of 25%, positive predictive value of 89.5%, and negative predictive value of 100% for TVUS diagnosis of adenomyosis. Endometriosis was histologically confirmed in all of the women who were included in the analysis as mentioned above.

There were no surgeries in the control group.

3.3. Sonographic Features Suggestive of Adenomyosis. The prevalence of sonographic features suggestive of adenomyosis in the study and control groups is presented in Table 2. There was a high overall prevalence (89.4%) of sonographic signs of adenomyosis in women undergoing laparoscopic surgery for endometriosis, much higher than in controls. The presence of any sonographic feature of adenomyosis was found to be more prevalent in the group of women with endometriosis as compared to the control group, despite their younger age. Features that were significantly more prevalent in women undergoing surgery compared to the control group were parallel shadowing linear striations, irregularity of the EMJ, and focal adenomyomas. The prevalence of any sonographic sign of adenomyosis was found to increase with age in both groups ($p < 0.01$). The presence of three or above and of five or above sonographic features was found to be more prevalent in the group of women with endometriosis as compared to the control group, and both were statistically significant ($p < 0.01$).

3.4. Association between Sonographic Features of Adenomyosis and Demographic Variables. The associations between sonographic features of adenomyosis and demographic variables using logistic regression for the three chosen models (without adjustment for variables, with adjustment for age, and with adjustment for age, smoking, BMI, and previous cesarean sections) are presented in Table 3. For all features but linear striations, the OR of having a specific feature was higher in women undergoing surgery as compared to the control group. The most significant association was found for irregularity of the EMJ, and focal adenomyomas, followed by parallel shadowing. After adjusting for age, all associations became markedly stronger.

In the study group, we could not find a significant association between the number of sonographic signs and the presence of clinical symptoms (Pearson Correlation not significant). In an attempt to determine the severity of adenomyosis based on ultrasound findings, we stratified the number of adenomyosis signs into 5 signs and above compared to fewer sonographic signs and performed the logistic regression again (see Table 4). Women with 5 or more

Table 2: Transvaginal ultrasound features suggestive of adenomyosis and their prevalence in women undergoing surgery for endometriosis versus controls.

	Endometriosis ($N = 94$)	Control ($N = 60$)	p
Asymmetrical myometrial thickening (%)	64 (68.1)	38 (63.3)	0.602
Myometrial cysts (%)	80 (85.1)	47 (78.3)	0.287
Parallel shadowing (%)	54 (57.5)	22 (36.7)	0.014*
Hyperechoic islands (%)	76 (80.9)	46 (76.7)	0.547
Linear striations (%)	25 (26.6)	27 (45.0)	0.023*
Irregular EMJ (%)	81 (86.2)	26 (43.3)	<0.001*
Focal adenomyomas (%)	36 (38.3)	7 (11.7)	<0.001*
Number of features, mean ± SD	4.4 ± 2.0	3.5 ± 2.3	0.009*
Any feature (%)	84 (89.4)	47 (78.3)	0.068
Number of features ≥ 3 (%)	82 (87.2)	41 (68.3)	0.004*
Number of features ≥ 5 (%)	54 (57.4)	21 (35)	0.007*

EMJ: endometrial-myometrial junction; SD: standard deviation. *Statistically significant finding.

features suggestive of adenomyosis had more than a 3-fold risk of suffering from infertility (OR = 3.19, $p = 0.015$, 95% CI; 1.25–8.17), a highly significant association. A similar finding was observed for women with 3 or more features suggestive of adenomyosis (OR = 2.51, $p = 0.007$, 95% CI; 1.28–4.9). However, there was no significant relationship with endometriosis severity at surgery. Of the women in the study group, 82.5% had normal patent tubes on both sides during surgery, eliminating mechanical infertility as a main cause.

4. Discussion

In this study, we found a very high overall prevalence (89.4%) of sonographic signs of adenomyosis in women undergoing laparoscopic surgery for endometriosis, much higher than in controls. We further found it to increase with age in both groups. The features that were found to be more significant were an irregular EMJ and focal adenomyomas, followed by parallel shadowing. An important finding was that women with more than 5 signs indicative of adenomyosis had a 3-fold increased risk of suffering from infertility, independent of the surgical severity of endometriosis.

Another interesting finding was that adenomyosis was reasonably prevalent in the controls as well, which may be attributed to the older age of the control group, as adenomyosis is known to be more prevalent in women in their late reproductive period. Despite this disparity in age between the study and control groups, adenomyosis was still found to be more common in the study group. In order to overcome this surprising finding, we reevaluated our data against 3 features or more and against 5 features or more. And indeed, in the study group, there was a greater prevalence than in the control group, in accordance with our prestudy expectations. In the control group, the features that were found to be the most prevalent were myometrial cysts and hyperechoic islands. It is plausible that these are early features of adenomyosis or a result of continued hormonal exposure as women age, whereas other features may be a marker of more advanced disease or of the association with endometriosis. These observations merit further study.

Previous studies addressing the prevalence of adenomyosis were performed on a surgical cohort with histological confirmation following hysterectomy. Until recently, MRI was generally considered to be the gold-standard imaging modality for diagnosis of adenomyosis. However, recent studies involving TVUS imaging showed higher accuracy and comparable detection rates [18, 24, 25, 28, 30, 31]. More recent studies [14, 22] have highlighted the coexistence of adenomyosis and deep infiltrating endometriosis in approximately 40–50% of women; the latter study also showed that related symptoms persisted after surgery when adenomyosis was present. Several studies have previously confirmed an association between adenomyosis and endometriosis; thus, this is not unexpected [14, 24, 32]. Hysterectomies are rarely performed for pain in modern clinical practice, mainly because most women seeking therapy are young and desirous of fertility and are operated on for indications of intractable severe pain or infertility issues. For this reason, histological confirmation of imaging findings is not always possible. Ultrasound and MRI are at present the only noninvasive modalities for preoperative diagnosis of adenomyosis. Ultrasound is more accessible, cheaper, and not inferior to MRI, leading to the opinion that TVUS should be the primary tool for the noninvasive diagnosis of adenomyosis and that surgical confirmation is not mandatory, particularly in women desirous of fertility [5, 12, 14].

The hypothesis that adenomyosis and infertility may be linked is gaining wider acceptance as increasing evidence to this effect is produced [6, 26, 27, 33–35]. A recent meta-analysis evaluated IVF outcomes in women with adenomyosis and found a 68% reduction in the likelihood of clinical pregnancy at in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI), and more than double the risk of miscarriage in these women [34]. The detrimental effect of adenomyosis on IVF/ICSI outcome seems to be both in reduced pregnancy rates and in increased early pregnancy

Table 3: The odds ratios for the association between sonographic features of adenomyosis in the study group versus the control group and demographic variables using logistic regression for the three chosen models: Model 1: unadjusted, without adjustment for variables; Model 2: adjusted for age; Model 3: adjusted for age, smoking, BMI, and previous cesarean sections.

	Model 1 (Unadjusted)				Model 2 (Adjusted for age)				Model 3 (Adjusted for age, smoking, BMI and CS)			
	OR	95% CI for OR		p	OR	95% CI for OR		p	OR	95% CI for OR		p
		LL	UL			LL	UL			LL	UL	
Any one feature	2.32	0.95	5.70	0.066	9.02	2.04	39.95	0.004*	13.01	2.46	68.78	0.003*
Asymmetrical thickening	1.23	0.62	2.44	0.543	1.98	0.79	4.98	0.144	2.20	0.85	5.71	0.105
Myometrial cysts	1.58	0.68	3.65	0.283	3.05	0.92	10.16	0.069	4.02	1.13	14.35	0.032*
Parallel shadowing	2.33	1.19	4.54	0.013*	5.84	2.29	14.91	<0.001*	6.28	2.37	16.65	<0.001*
Hyperechoic islands	1.28	0.58	2.83	0.533	2.28	0.76	6.86	0.141	2.47	0.77	7.86	0.127
Linear striations	0.44	0.22	0.88	0.020*	0.72	0.30	1.74	0.471	0.64	0.25	1.60	0.344
Irregular EMJ	8.15	3.75	17.72	<0.001*	20.00	5.78	69.26	<0.001*	25.47	6.74	96.25	<0.001*
Focal adenomyomas	4.70	1.93	11.45	0.001*	7.87	2.69	22.98	<0.001*	7.69	2.54	23.28	<0.001*

EMJ: endometrial-myometrial junction; OR: odd's ratio; LL: lower limit; UL: upper limit. *Statistically significant finding.

Table 4: Univariate analysis of the associations between demographic data, clinical symptoms, disease severity, and number of sonographic features of adenomyosis in the study group.

	Any adenomyosis feature				Five or above features			
	OR	95% CI for OR		p	OR	95% CI for OR		p
		LL	UL			LL	UL	
Age	1.14	1.01	1.29	0.031	1.04	0.97	1.11	0.291
BMI	1.18	0.95	1.46	0.123	1.03	0.94	1.13	0.520
Previous delivery	3.64	0.73	18.15	0.115	0.67	0.3	1.57	0.373
Previous cesarean	1.36	0.16	11.77	0.782	1.04	0.3	3.56	0.947
Dysmenorrhea	1.43	0.15	13.22	0.755	0.99	0.21	4.71	0.993
Dyspareunia	0.41	0.08	2.06	0.280	0.63	0.26	1.52	0.305
GI complaints	0.46	0.11	1.91	0.286	1.32	0.57	3.03	0.515
Urinary complaints	1.68	0.33	8.52	0.529	0.88	0.35	2.2	0.789
Infertility	1.21	0.28	5.21	0.800	**3.19**	**1.25**	**8.17**	***0.015**
ASRM score	1	0.98	1.02	0.873	**1.01**	**1**	**1.02**	***0.046**
ASRM stage	0.91	0.5	1.68	0.772	1.32	0.91	1.9	1.32

ASRM: American Society for Reproductive Medicine; BMI: body mass index; OR: odd's ratio; GI: gastrointestinal; OR: odd's ratio; LL: lower limit; UL: upper limit. *Statistically significant finding.

loss. Indeed, in our study there was a high rate of IVF treatments before surgery in the study group, which could have also been related to the presence of adenomyosis. Age may also have been a detrimental factor, although in general, the women were young. Specific treatment modalities aimed at alleviating adenomyosis and endometriosis that conserve uterine and ovarian function are important considerations in women desiring fertility. Accurate preoperative assessment of adenomyosis in women with endometriosis scheduled for surgery is imperative in order to preserve and plan reproductive management. Screening for adenomyosis before embarking on medically assisted reproductive procedures should be encouraged in this group with a high risk for infertility. Conversely fertility sparing surgical methods should be implemented in general and particularly if adenomyosis is found in a woman operated on for endometriosis.

The strength of our study is in the fact that a single operator specifically dedicated to endometriosis evaluation performed all of the TVUS examinations using a high frequency transvaginal probe and utilizing known diagnostic criteria, for both the study and the control group. The morphological diagnostic features that we used have been previously described as valid criteria for noninvasive diagnosis of adenomyosis [13–17]. These features were recently described in a statement paper by the Myometrial Pathology Using Ultrasonography Consensus Group (MUSA) [30]. A further strength of this study is our control group of healthy women, from which women who may have had symptoms suggestive of endometriosis were excluded. Additionally, we performed the evaluation for multiple features of adenomyosis in order to increase accuracy and overcome potential bias, particularly the one arising from the age discrepancy discussed above.

A weakness of this study is the retrospective design and the limited availability of histological confirmation, as these were mostly young women seeking fertility which influenced the low hysterectomy rates. However, the correlation between ultrasound diagnosis of adenomyosis and histological diagnosis in the women who did undergo hysterectomies was good and strongly supports the known validity of this modality for preoperative diagnosis, even though the number of hysterectomies was small. As stated previously, the recent consensus [30] implies that ultrasound can be a definitive diagnosis without the need for histological confirmation. Furthermore, the comparison with the control group addresses this caveat. There may be a slight selection bias in our study. The prevalence that was found is high, most probably because this is a highly selected population of women with severe endometriosis and severe symptoms that were selected for surgical treatment and for whom conservative management was not an option.

In conclusion, sonographic features of adenomyosis are highly prevalent in women undergoing surgery for endometriosis. A large number of sonographic signs of adenomyosis were found to be associated with a higher risk of suffering from infertility, regardless of endometriosis severity. This can be taken to mean that endometriosis severity is not the only predictor of fertility in these women. Furthermore, this may bear direct implications on tailoring patient-specific treatments, both before and after the operation, such as secondary prevention by hormonal therapy or choice and timing of fertility treatments. It would be interesting to conduct a prospective study utilizing this potential scoring system for adenomyosis in symptomatic and asymptomatic women, in order to confirm these findings. Further study may be indicated in order to evaluate the relationship between age and sonographic features of adenomyosis in a healthy control group, and to compare women with endometriosis undergoing surgery to those who do not. We plan to investigate these issues in future research.

Conflicts of Interest

There are no conflicts of interest or industrial affiliations.

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Review Article

The Rising Phoenix-Progesterone as the Main Target of the Medical Therapy for Leiomyoma

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Leiomyomas, also known as uterine fibroids, are a common benign tumor in women of reproductive age. These lesions disrupt the function of the uterus causing menorrhagia and pelvic pressure as well as reproductive disorders. These women pose a true challenge for clinicians in the attempt of choosing the suitable treatment for each patient. Patient's age, interest in fertility preservation, and leiomyoma location and size are all factors to be taken into account when deciding upon the preferable therapeutic option. For the past few decades, surgical treatment was the only reliable long-term treatment available. A variety of surgical approaches have been developed over the years but these developments have come at the expense of other treatment options. The classical medical treatment includes gonadotropin-releasing hormone (GnRH) agonists and antagonists. These agents are well known for their limited clinical effect as well as their broad spectrum of side effects, inspiring a need for new pharmacological treatments. In recent years, promising results have been reported with the use of selective progesterone receptor modulators (SPRM). Long-term clinical trials have shown a reduction in bleeding and shrinkage of leiomyoma mass. These results instill hope for women suffering from symptomatic leiomyomas seeking an effective, long-term medical option for their condition.

1. Introduction

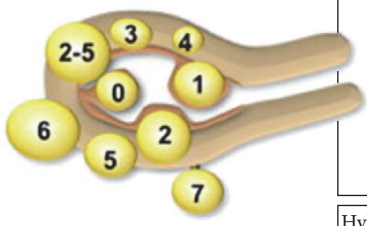
Uterine leiomyomas, also called fibroids, are the most common form of benign gynecological tumors [1, 2]. These are hormone sensitive tumors with a clonal origin, derived from myometrial smooth-muscle cells and connective tissue fibroblasts. Leiomyomas characteristically present as well encapsulated fibrotic tissue within the wall of the uterus occurring in 77% of all women with a higher incidence in African-American women [3–6].

Leiomyomas are commonly classified into 3 subgroups according to their location in the uterus: subserosal, intramural, and submucosal. A detailed classification system has been published by FIGO (International Federation of Gynecology and Obstetrics) (Figure 1), with specific attention to the fibroid's location [7].

The most recognized risk factors for the development of leiomyomas are early menarche, nulliparity, increased frequency of menses, history of dysmenorrhea, family history of leiomyomas, African descent, obesity, age (peak incidence at 40–50), and medical conditions such as diabetes and hypertension [8–11]. Behavioral attitudes such as diet with high consumption of meat or alcohol can also increase the risk, as opposed to smoking that decreases the risk [12–14].

In many cases leiomyomas are asymptomatic and are diagnosed incidentally on clinical examination or imaging. Only 20–50% of women suffer from a variety of symptoms, usually in accordance with the location and size of the mass [15, 16]. The symptoms are sometimes significant and can be divided into different categories: menorrhagia, space occupying manifestations, and reproductive disorders [17–21]. Women suffering from symptomatic leiomyomas have a significant lower health related quality of life and productivity: 43% will suffer an impact on sexual life, 28% will suffer an impact in performance at work, and 27% will be affected by the symptoms as a social matter in relationship and family [10, 22]. An improvement in quality of life has been shown

Leiomyoma subclassification system



SM (submucosal)	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
O (others)	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Others (specify, e.g., cervical and parasitic)
Hybrid leiomyomas (impact on both endometrium and serosa)	Two numbers are listed and separated by a hyphen; by convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2–5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively

Figure 1: FIGO leiomyoma subclassification system.

following leiomyoma treatment, emphasizing the great need for a wide spectrum of therapeutic options.

Until recently, despite a great deal of research involving investment of substantial resources the goal of finding an effective medical treatment has eluded the scientific community. Nowadays, uterine leiomyomas remain the primary indication for hysterectomy in women of reproductive age in America [23].

Recently, a major change and hope have emerged. Selective progesterone receptor modulators (SPRM) have been offered as effective medical therapy for leiomyomas, with minimal side effects and promising long-term results. In this paper, we review these new pharmacological modalities and the opportunities they offer to a large population of women in need of alternative medical treatments.

2. Etiology

Despite years of research the pathogenesis of leiomyomas remains unclear. Clearly, enhancement of extracellular matrix (ECM) deposition plays an important role in the formation of uterine fibroids [24]. Norian et al. hypothesized that mechanical stress may set in motion a cascade of events leading to excessive ECM deposition which may bring about formation of uterine fibroids [25]. Several molecular pathways as well as genetic factors have been suggested as key elements in the development of uterine fibroids and have evoked much debate regarding possible treatments for inhibiting uterine fibroid growth. Tyrosine kinase inhibitors (TKI), cyclin-dependant kinase (CDK) inhibitors, aromatase inhibitors, and antiproliferative agents are only a partial list of biological mechanisms targeted by pharmaceutical solutions for the treatment for uterine fibroids [26–29]. Unfortunately, though in theory most of these treatments have biological merit to them, clinical results have been disappointing.

Over the years estrogen was considered to be the main culprit responsible for their growth. Recent studies have made it clear that progesterone too is an important player in leiomyoma growth. The clinical observations that have traditionally supported the estrogen hypothesis also support the hypothesis that progesterone is involved in the pathogenesis of leiomyomas. Similar to estrogen levels, progesterone levels are elevated during the reproductive years, decreased during menopause, and suppressed during GnRH agonist therapy [30]. One of the first reports to connect between progesterone and leiomyomas was in 1949 when Segaloff et al. observed increased cellularity in the histologic structure of leiomyomas in 6 patients treated with 20 mg progesterone daily during 30–128 days [31]. Later, Tiltman showed a significantly higher mitotic activity in leiomyomas of woman who were treated with medroxyprogesterone acetate compared to an untreated group [32]. Kawaguchi et al. in their study investigated the influence of the menstrual cycle on the mitosis rate of uterine fibroids [33]. They reported a significantly higher mitotic count in the secretory phase, suggesting that fibroid growth is affected by progesterone. In another study Lamminen et al. compared proliferative activity of uterine fibroids of different women, showing that, in postmenopausal women without hormone replacement therapy (HRT) or with estrogen only as HRT, low proliferative activity was demonstrated [34]. On the other hand, postmenopausal woman treated with estrogen and progesterone as HRT showed a proliferating index equal to that observed in premenopausal women. Brandon et al. demonstrated that compared to adjacent myometrium there is an increase in progesterone receptor messenger ribonucleic acid expression, as well as progesterone receptor protein level in leiomyoma tissue [35]. In the same study a significantly higher rate of the proliferation antigen Ki-67 was found in leiomyoma tissue, suggesting that amplified progesterone-mediated signaling is instrumental in the abnormal growth of these tumors.

In addition to the biochemical and histological evidence supporting the role for progesterone in the pathogenesis of leiomyomas, there is compelling clinical evidence supporting this hypothesis. In 1961 Mixson and Hammond reported that norethynodrel causes rapid but reversible enlargement of

uterine leiomyomas [36]. Friedman et al. as well as Carr et al. demonstrated that medroxyprogesterone acetate inhibits the ability of GnRH agonist-induced hypoestrogenism to shrink uterine leiomyomas [37, 38]. In another prospective trial Friedman et al. suggested that high-dose norethindrone can reverse the effectiveness of GnRH agonist-induced leiomyoma shrinkage in a dose-dependent action [39].

In 2013, Bulun suggested a new theory, showing the influence of smooth-muscle stem cells and progesterone in the development of leiomyomas [40]. Based on these assumptions it seems as though genetic defects on the cellular level of the myometrial smooth-muscle are key in leiomyoma formation. Point mutations in mediator complex subunit 12 (MED12) as well as in high-mobility group AT hook 2 (HMGA2) have been linked with uterine fibroid development and may be the preliminary step leading to tumorigenesis [41, 42]. The genetic changes installed by this pivotal incident may later lead to the modification of signal pathway transduction involving beta-catenin and tumor growth factor-beta (TGF-beta). These proteins are thought to regulate cell proliferation ultimately leading to clonal expansion and uterine fibroid growth. These smooth-muscle cells remain sensitive to estrogen and progesterone and are triggered during receptor activation by the appropriate ligand.

The receptor for progesterone presents a potential target for pharmacological treatment of leiomyomas. When activated it acts as an important transcription factor for uterine fibroid growth [43]. When bound by the antiprogestin RU-486 the progesterone receptor begins a series of events ending in the increase of Kruppel-like factor 11 (KLF11). Increased levels of this tumor suppressor gene have been linked to inhibition of fibroid proliferation [44]. At the cellular nuclear level binding of progesterone to the progesterone receptor has also been shown to increase levels of the antiapoptotic protein B cell lymphoma-2 (BCL2) which in turn stunts cell death and leads to fibroid growth [45].

The full effect of the progesterone-progesterone receptor complex on stem cells as well as on differentiated cells in uterine fibroids is still poorly understood. It is suspected that binding of progesterone to the progesterone receptor brings on changes at the genetic and epigenetic level leading to propagation and proliferation of these benign tumors [40]. Due to the pivotal role of progesterone in the pathogenesis of leiomyoma growth, researchers as well as pharmaceutical companies have focused on finding compounds that might inhibit its effect. These efforts have brought forth the selective progesterone receptor modulators (SPRM) which so far have shown promising results.

3. Surgical Therapy

Choosing the appropriate treatment for uterine fibroids is not an easy task. Many parameters need to be taken into account including patient age, desire for fertility preservation, and the ability to undergo surgery [46–48]. To date, surgery remains the main treatment option for symptomatic women with uterine leiomyomas [49, 50]. Surgical treatment options include hysterectomy, myomectomy by laparoscopy, robotic surgery, or laparotomy as well as myomectomy by hysteroscopy. Prospective trials regarding surgical techniques and long-term outcomes with evaluation of symptoms are scarce making it difficult to recommend one treatment option over the other. The risks and benefits for each treatment option need to be presented to the patient enabling her to reach an informed decision with proper coordination of expectations.

Albeit the many surgical techniques available today, hysterectomy still remains the definitive treatment option for uterine fibroids. Suitable for patients for whom fertility is no longer an issue to be taken into account, hysterectomy offers low reintervention rates as well as high rates of symptom relief [51]. Hysterectomy does have some notable downsides. Published in 1994, the Main's Women's Health Study mentioned that only 72% of women reported improvement in symptoms caused by uterine fibroids [52]. In other studies abdominal hysterectomy was shown to correlate with higher rates of major complications compared to other invasive treatments such as uterine artery embolization [53, 54]. Hysterectomy no doubt will continue to be the treatment of choice for certain women though there is place for randomized controlled studies with long-term follow-up which will hopefully help assess the true value of this procedure.

In cases where fertility preservation is desired myomectomy remains the treatment of choice [55]. The abdominal approach for this procedure includes laparotomy and laparoscopy as well as robotic methods or when possible hysteroscopic myomectomy. Though considered technically challenging, laparoscopic myomectomy presents several advantages when compared to open myomectomy. Donnez et al. as well as several others showed faster recovery with less postoperative morbidity for patients undergoing laparoscopic myomectomy compared to the open approach. These advantages did not come at the expense of reproductive outcomes as well as recurrence rate which were similar for the two procedures [56, 57].

4. Medical Therapy

4.1. Current Medical Therapy. Over the years various medical treatments have been suggested based on the biological understanding of fibroid growth. Most treatments to this day have fallen short in giving a true long-term solution for women suffering from uterine fibroids. Two of the most common therapies are GnRH agonists or antagonists and aromatase inhibitors.

4.1.1. GnRh Agonists and Antagonists. Until recently, GnRH agonists have been the most efficient pharmacological treatment for leiomyomas. GnRH agonists have a direct action on the pituitary, inducing downregulation and desensitization of the GnRH receptors, producing a hypogonadotropic state with consequent reduction in estradiol and progesterone [16]. GnRH agonists were found to decrease uterine bleeding, improve hematologic parameters, manage symptoms of menometrorrhagia, dysmenorrhea, and pelvic discomfort, and reduce uterine and leiomyoma size [58]. Nevertheless, this treatment cannot be given for a long period of time due to the many side effects that accompany it including bone

loss, hot flashes, sleep disturbance, vaginal dryness, myalgia, arthralgia, and possible impairment of mood and cognition [37].

A review published in 2015 found low to moderate quality evidence that add-back therapy with tibolone, raloxifene, estriol, and ipriflavone helps to preserve bone density and that medroxyprogesterone acetate (MPA) and tibolone may reduce vasomotor symptoms. Larger uterine volume was an adverse effect associated with some add-back therapies (MPA, tibolone, and conjugated estrogen) [59]. Upon cessation of treatment there is a resumption of menses and pretreatment uterine volume [60]. Numerous side effects and temporary benefit have caused GnRH agonists to be mainly used in the preoperative setup. A systemic review found that the use of GnRH agonists for three to four months prior to fibroid surgery reduces both uterine volume and fibroid size. GnRh agonists are beneficial in the correction of preoperative iron deficiency anemia (if present) and reduce intraoperative blood loss. If uterine size is such that a midline incision is planned, this can be avoided in many women with the use of GnRH agonist. For women undergoing hysterectomy, a vaginal procedure is more likely following the use of these agents [60]. Another drawback of this therapy is that prior to the downregulation of the GnRH receptors there is an increase in estrogen level (flare-up) that might aggravate symptoms.

GnRH-antagonists achieve similar clinical results as the agonists but with more rapid onset due to the lack of initial flare-up observed with GnRH agonists. However, these agents are not available as long-term treatments, require daily injections, and have not been adopted as a common therapy for leiomyomas [61].

4.1.2. Aromatase Inhibitors. The inhibition of the aromatase enzyme has been speculated to be a key mechanism in regulating hormone-dependent fibroid growth by inhibiting the production of estradiol. Estradiol, through the estrogen receptor α, induces the production of progesterone receptor which is essential for the response of fibroid tissue to progesterone; this response includes increased cell survival, cell proliferation, and enhancement of extracellular matrix [40]. Yet, a recent Cochrane review on the use of aromatase inhibitors concluded that there was no evidence to support the use of these agents as medical therapy for treating uterine fibroids [62].

4.2. Selective Progesterone Receptor Modulators (SPRM). SPRM are a family of substances which are known to incorporate both an agonist and an antagonist response on the receptor for progesterone (Figure 2) [16]. This response is mediated by many coreceptors and cofactors and has been shown to bare a favorable effect on the growth and development of leiomyomas [43, 63, 64]. This rationale has led pharmaceutical companies to invest in the research of these compounds leading to an array of products meant to stunt the growth of leiomyomas. In a recent publication we elaborate on their great potential and the important role these compounds may play in the near future [65]. Asoprisnil, mifepristone, and ulipristal acetate are a few examples of medications that were shown to be effective in decreasing the size of leiomyomas as well as reducing symptoms correlated with leiomyomas [66–70].

Ulipristal acetate is the most recent SPRM and has been under extensive investigation in the attempt to analyze its success in the treatment of uterine fibroids. This compound evokes an antiproliferative effect on leiomyoma cells as well as having a good safety profile with an easy to use regimen of one pill per day [71, 72]. Hence, it is easy to understand the enthusiasm in the scientific community regarding this potential treatment. In the PEARL I trial patients with symptomatic leiomyomas were treated with either placebo, 5 mg or 10 mg of ulipristal acetate for a duration of 13 weeks [73]. Results of this study showed a clear advantage for treatment with ulipristal acetate with control of menstrual bleeding in 92% of women who received a dose of 10 mg ulipristal acetate versus 19% in the placebo group. There was no difference between the groups regarding adverse effects. Leiomyoma volume, measured by magnetic resonance imaging, was reduced by a median reduction percentage of 21.2% for patients treated with 10 mg ulipristal acetate. The treatment's efficacy was shown with both objective (leiomyoma size) and subjective (patient discomfort) measures with encouraging results.

Later, a study was conducted comparing the efficacy of ulipristal acetate and a GnRH agonist. The PEARL II study, a randomized prospective trial, included women suffering from symptomatic uterine fibroids who received either an intramuscular injection of leuprolide acetate or treatment with ulipristal acetate (5 or 10 mg) [74]. Menstrual bleeding was controlled for patients who received 10 mg and 5 mg ulipristal acetate in 98 and 90 percent, respectively. Mean time to amenorrhea for these 2 groups was 5 and 7 days, respectively. For the leuprolide acetate group, control of menstrual bleeding was achieved in 89% with mean time to amenorrhea being 21 days. The difference in mean time to amenorrhea was statistically significant between the groups. Regarding reduction in uterine size, leuprolide acetate was superior when compared to ulipristal acetate. Hot flushes were a noteworthy side effect documented in 40% of patients treated with leuprolide acetate as opposed to 10% of women in the ulipristal acetate group. Conclusions of this study include ulipristal acetate being noninferior to leuprolide acetate with regard to the therapeutic effect on symptomatic leiomyomas with fewer side effects. In the following trial (PEARL III) ulipristal acetate was evaluated regarding its ability to induce a long-term effect for treatment of uterine fibroids. Two 12-week courses of treatment with ulipristal acetate 5 and 10 mg were administered to 451 patients enrolled in the study [64]. Amenorrhea was achieved in the 5 and 10 mg groups in 62 and 73 percent, respectively. During 2 treatment courses over 80% of patients achieved controlled bleeding. Median reductions from baseline in fibroid volume were 54 and 58 percent for the 5 mg and 10 mg groups, respectively. The treatment was well tolerated with under 5% of women abandoning treatment due to adverse effects. The investigators summarize that repeated 12-month treatment courses are effective in control of bleeding and reduction of fibroid size as well as improvement of quality of life (QOL) in patients suffering from symptomatic uterine fibroids [64, 71].

Fertility is a prominent issue in women with leiomyomas. Data regarding 21 patients who tried to get pregnant after

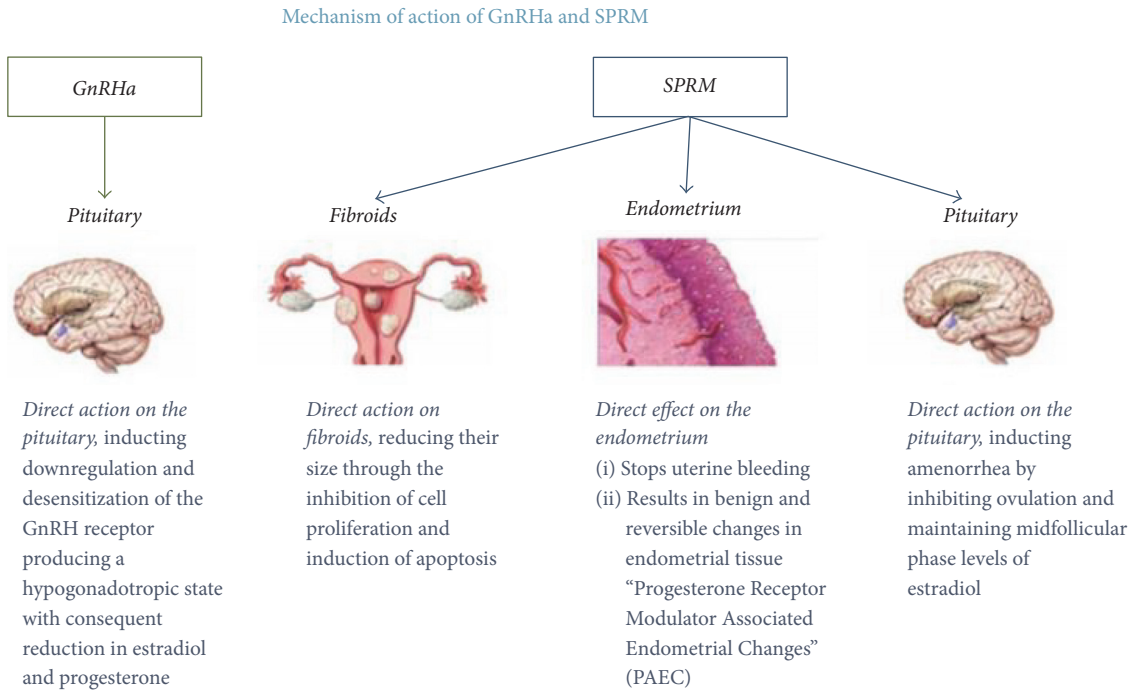


Figure 2: Mode of action of GnRH agonists and SPRM (selective progesterone receptor modulators). GnRH agonists have a direct impact on the pituitary. SPRM have a direct impact on fibroids, endometrium, and the pituitary [16].

UPA therapy (PEARL II and PEARL III trials) [75] showed that 15 women (71%) managed to conceive, resulting in a total of 18 pregnancies. Six women had a miscarriage and 12 pregnancies resulted in the live birth of 13 healthy babies. The high miscarriage rate may be explained by the median age of the population (38 years). Despite the hormonal changes expected during pregnancy no regrowth of leiomyomas was noted in pregnant women after cessation of UPA treatment.

Earlier this year, a new multicenter, prospective, non-interventional study (PREMYA) was published. A total of 1473 women with moderate to severe symptoms who received preoperative treatment with UPA (5 mg daily for 3 months) were enrolled. Data was collected every 3 months over a period of 12 months from the time treatment was discontinued. All patients were scheduled for surgery but only 38.8% finally underwent surgery. Physician assessment indicated that 60.1% of patients were either "much" or "very much" improved at 3 months.

A good safety profile was shown. Only one severe adverse effect was mentioned. It involved a diagnosis of leiomyosarcoma after hysterectomy. Only 56 (3.8%) patients stopped taking the medication due to side effects. This study reinforces previous results showing that quality of life and pain are highly improved by UPA treatment while maintaining a good safety profile.

In conclusion, SPRM are changing the way clinicians treat uterine fibroids. While surgical therapy remains the only definitive treatment, SPRM offer caregivers a viable option for treatment of this common pathology.

Disclosure

H. H. Chill and M. Safrai are co-first authors.

Conflicts of Interest

There were no conflicts of interest.

Authors' Contributions

H. H. Chill and M. Safrai contributed equally to this work.

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Review Article

Hysteroscopic Morcellation of Submucous Myomas: A Systematic Review

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Hysteroscopic surgery is the actual gold standard treatment for several types of intrauterine pathologies, including submucous myomas (SMs). To date, the availability of Hysteroscopic Tissue Removal systems (HTRs) opened a new scenario. Based on these elements, the aim of this article is to review the available evidence about HTRs for the management of SMs. We included 8 papers (3 prospective studies and 5 retrospective studies). A total of 283 women underwent intrauterine morcellation of SM: 208 were treated using MyoSure and 75 using Truclear 8.0. Only 3 articles reported data about procedures performed in outpatient/office setting. Only half of the included studies included type 2 SMs. HTRs significantly reduced operative time compared to traditional resectoscopy in some studies, whereas others did not find significant differences. Despite the availability of few randomized controlled trials and the cost of the instrument, according to our systematic review, the use of HTRs seems to be a feasible surgical option in terms of operative time and complications. Nevertheless, the type of SM still remains the biggest challenge: type 0 and 1 SMs are easier to manage with respect to type 2, reflecting what already is known for the "classic" hysteroscopic myomectomy.

1. Introduction

The progressive improvement of hysteroscopic instruments and the standardization of techniques allowed feasible and daily management of submucous myomas (SMs). Hysteroscopic myomectomy is usually performed with a progressive slicing of the intracavitary portion of the SM, a subsequent "cold loop" pushing of the intramural part (to preserve the pseudocapsule), and, finally, a slicing resection of it [1–3]. As was widely reported, a careful and conscious management of uterine myomas improves not only symptoms, but also fertility outcomes [4, 5].

To date, the availability of Hysteroscopic Tissue Removal systems (HTRs) opened a new scenario for hysteroscopic myomectomy: indeed, the learning curve for resectoscopic management of SM is challenging for both the residents and specialists and may lead also to severe complications [6]. In this regard, HTRs may reduce the learning curve and complication rate of hysteroscopic myomectomy for SM with respect to traditional resectoscopy.

The use of morcellators in gynecologic surgery started for myomectomy and hysterectomy first in laparoscopy; however in 2014 the U.S. Food and Drug Administration warned against the use of laparoscopic power morcellators for the

risk of spreading an unsuspected cancer [7]. Nevertheless, this Safety Communication does not affect HTRs. HTRs consist of 2 metal, hollow, rigid, and disposable tubes with a wide range of diameters adaptable to the use of 5 to 9 mm hysteroscopes. Different HTRs are commercially available: Truclear 8.0 (Medtronic, Minneapolis, Minnesota), Truclear 5C (Medtronic, Minneapolis, Minnesota), and MyoSure (Hologic, Marlborough, Massachusetts). As recently summarized by Noventa et al. [8], Truclear 8.0 has a diameter of 8 mm and is introduced into the uterine cavity with a 9 mm rigid sheath; Truclear 5C hysteroscopy system incorporates a 2.9 mm rotatory-style blade through a 5 mm, 0° hysteroscope; MyoSure is introduced into the uterus through a 6 or a 7 mm, 0°, continuous flow hysteroscope. All these devices work with physiologic saline solution as distension and irrigation media, instead of the electrolyte-free solutions used for monopolar high-frequency resectoscopy.

Considering that data published so far do not allow drawing a firm conclusion, the aim of this article is to review the available evidence about the role of HRTs for the management of SMs.

2. Materials and Methods

We performed the database search on Scopus, PubMed/MEDLINE, and Science Direct. We searched with "Hysteroscopic Tissue Removal system", "Intrauterine morcellator", and "Hysteroscopic morcellator". We considered eligible original articles (randomized, observational, retrospective studies) about SM management through the use of HTRs, excluding case reports and video articles, published between 2000 and 2016 in English and French languages.

Titles and/or abstracts of retrieved articles were screened independently by two authors (F. S. and G. V.) to identify studies that potentially meet the inclusion criteria outlined above. The full texts of these potentially eligible studies were retrieved and independently assessed for eligibility by other two authors (B. C. and A. M. C. R.). Any disagreement between them over the eligibility of particular studies was resolved through discussion with a third author (A. S. L.). A standardized, prepiloted form was used to extract data from the included studies for assessment of study quality and evidence synthesis. We selected information about study design, type of SMs, type of HTRs, operative time, fluid balance, and operative outcomes. Studies providing ambiguous or insufficient data or not quantifiable outcomes were excluded from the current analysis.

3. Results

Using the reported search strategy, we identified 19 items for "Hysteroscopic Tissue Removal system", 14 items for "Intrauterine morcellator", and 27 items for "Hysteroscopic morcellator". After exclusion of 14 duplicates, we screened 46 items and further excluded 4 of them because they were case reports and/or video articles. The remaining 44 items were selected and each full text was carefully evaluated, in order to select only relevant information (hysteroscopic morcellation of submucous myoma). Since 34 full texts were out of purpose, in the current systematic review, we included the remaining 8 papers [9–16] that met the abovementioned inclusion criteria (the search strategy is summarized in Figure 1). As summarized in Table 1, 3 were prospective studies [9–11] and 5 were retrospective [12–16]. In all articles, patients' mean age was above 40 years. The authors used MyoSure in 5 articles [9, 11–14] and Truclear 8.0 in the remaining 3 [10, 15, 16]. The total retrieved cases of SM treated with HTRs were 283: 208 cases were performed using MyoSure devices, whereas 75 were performed using Truclear 8.0. Interestingly, only two articles reported data about procedures performed in outpatient/office setting [9, 13], whereas all the other collected cases were performed in operating theatre. Among the included studies, less than half [11, 13, 14] included data about type 2 SM. All the data about operative time, fluid deficit, complications, and main outcomes are reported in Table 1 and will be discussed in the next section.

4. Discussion

Operative time data were available in half of the included studies [10, 12, 14–16] and, in any case, were extremely variable: minimum average time was 10.6 min, for van Dongen et al. [10]; maximum was 36.6 min for Lee and Matsuzono [12]. The first data seems more reliable because it came from a randomized controlled trial, while other available data about operative times came from retrospective studies. Similarly, fluid deficit data were available only in 6/8 articles: they are almost overlapping (or at least comparable) in only 4 studies [10, 13, 15, 16], between an average of 409 mL in the only RCT [10] and 660 mL in a retrospective study [15]; only in 2 articles [11, 12], fluid deficit was higher, between an average of 880 mL [11] and 1800 mL. The article from Arnold et al. [11] that reports a fluid deficit of 880 mL is a prospective study with a cohort of 102 cases. In the article of Rubino and Lukes [9], fluid deficit for all patients is not available, but a deficit nearly 4 L has been reported at least in one patient, which is contrary to hysteroscopic fluid management guidelines [17]. In this regard, usually a maximum fluid deficit of 1000 mL is recommended, but with the advent of bipolar electrosurgical systems in traditional resectoscopy and in HTRs a deficit of 2500 mL of isotonic solution is well tolerated by healthy women [18]. The mean operative time is 22,6 min and the mean fluid deficit is 730 mL. All the articles did not report significant intra- or postoperative complications. These data are of paramount importance, since it was clearly demonstrated that bleeding rate is associated with the degree of SM intracavitary development [19]. Only 3 retrospective studies and one small cohort prospective study compared resectoscopy to HTRs, so data are extremely limited. In some studies that compared intrauterine morcellation to resectoscopy, HTRs significantly reduced operative time [10, 12, 15], whereas others did not find significant differences [14]. In addition, the overall complete resection rate of SMs using HTRs seems to be comparable to resectoscopy [11, 14]. In detail, authors of the retrospective studies reported reduced operative times with HTRs compared to resectoscopy; Lee and Matsuzono found no significant differences in overall patient satisfaction and improvement in hemoglobin level

Table 1: Relevant data of retrieved studies.

Authors, year	Type of study	Enrolled cases	Mean age	Type of myomas	Type of HTRs	Mean operative time (min)	Mean fluid deficit (mL)	Main findings
Rubino and Lukes, 2015 [9]	Randomized, prospective, comparative setting clinical trial	42 myomas	41.4 (overall, including also other pathologies)	Type 0 or 1 myomas > 1.5 and <3.0 cm	MyoSure	NA	NA	(1) 28 myomectomies were performed in office setting and 14 in ambulatory surgical center setting. (2) The mean percentage of pathology removed was 95.9 ± 6.8%. (3) Both Uterine Fibroid Symptom-Quality of Life and Health-Related Quality of Life improved significantly 12 months after procedure. (4) A fluid deficit of nearly 4 Lt was reported in at least one patient.
van Dongen et al., 2008 [10]	Prospective randomized controlled study	10 myomas	49	Type 0, type 1	Truclear 8.0	10.6	409	The use of the HTRs reduced operating time more than 8 min in comparison to conventional resectoscopy.
Arnold et al., 2016 [11]	Prospective cohort study	102 myomas	43	29 type 0, 38 type 1, 17 type 2, 18 not documented	MyoSure	NA	880	63 complete resection of pathology at the end of the procedure: 18 type 0, 27 type 1, and 11 type 2 myomas.
Lee and Matsuzono, 2016 [12]	Retrospective study	13 myomas	NR	2 patients with myoma protrusion < 60%, 11 patients > 60%; 9 small (≤3 cm) myomas, 4 large (>3 cm) myomas	MyoSure	36.6	1005	(1) No significant differences in overall patient satisfaction and improvement in hemoglobin level between intrauterine morcellation and resectoscopy at 3-month follow-up. (2) HTRs significantly reduced operative time.
Rajesh and Guyer, 2015 [13]	Retrospective study	17 myomas	58.6	Type 0, type 1, and type 2; size 1–5 cm	MyoSure	NA	495.3	(1) All patients had successful removal of pathology apart from two partial myomectomies (calcified fibroids) and one failed MyoSure for patulous cervix. (2) No complications occurred. (3) Intrauterine morcellation is feasible also in outpatient setting.

Table 1: Continued.

Authors, year	Type of study	Enrolled cases	Mean age	Type of myomas	Type of HTRs	Mean operative time (min)	Mean fluid deficit (mL)	Main findings
Hamidouche et al., 2015 [14]	Retrospective study	34 myomas	40.8	Type 0, type 1, and type 2	MyoSure	30.8	NA	No significant differences for mean operative time, complete resection rate, adverse events, and postoperative adhesion between HTRs and bipolar loop resection.
Emanuel and Wamsteker, 2005 [15]	Retrospective study	28 myomas	44.6	15 type 0, 13 type 1	Truclear 8.0	16.4	660	(1) Significant reduction of operative time for HTRs compared to resectoscopy. (2) No complications.
Hamerlynck et al., 2011 [16]	Retrospective study	37 myomas	45	Type 0, type 1	Truclear 8.0	18.2	440	(1) All procedures were uneventful. (2) Implementation of the HTRs for removal of type 0 and 1 myomas ≤ 3 cm, and removal of polyps appears safe and effective.

HTRs: Hysteroscopic Tissue Removal systems; NA: not available.

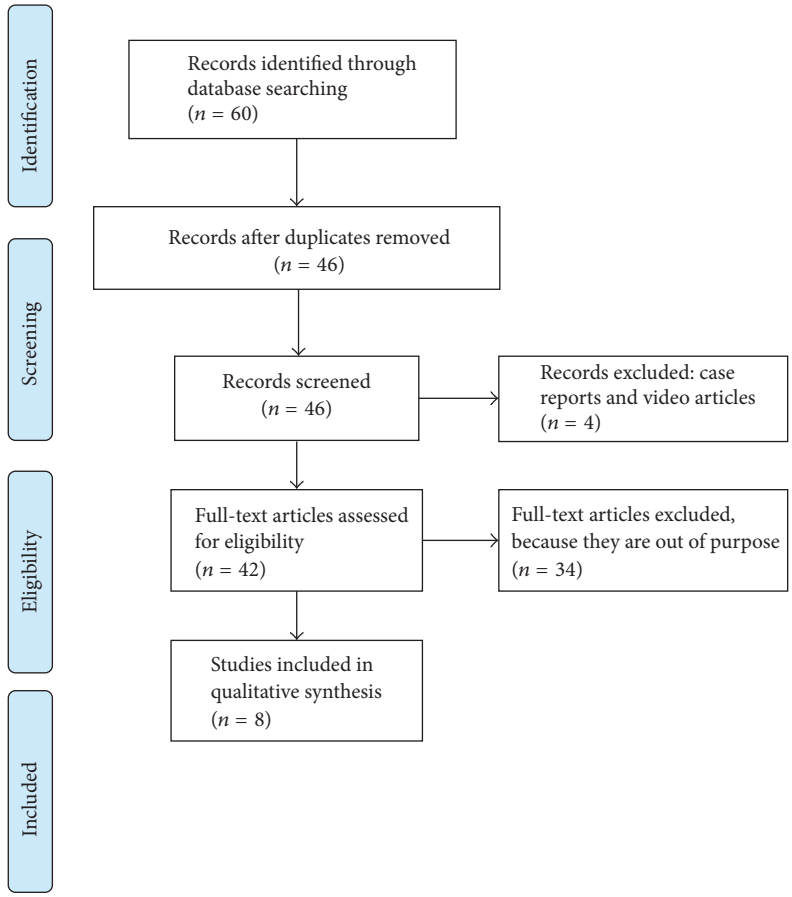

Figure 1: Searching strategy. Adapted from Moher D., Liberati A., Tetzlaff J., Altman D. G., and The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.

between the two methods at 3-month follow-up [12], whereas Hamidouche et al. do not signaled differences for mean operative time, resection rate, adverse events, and intrauterine postoperative adhesions in a larger cohort (34 myomas) with respect to the precedent study (13 myomas) [14]. Finally, recent data suggest that both Uterine Fibroid Symptom-Quality of Life and Health-Related Quality of Life improve significantly 12 months after myomectomy using HTRs [9].

5. Conclusion

Despite the introduction of HTRs in the clinical practice several years ago, published data about their use for the management of SMs are so far extremely limited, especially because this technique was not so attractive for surgeons, probably due to the large consent gained through the time by traditional resectoscopy. The available studies differ significantly regarding methodology and inclusion and exclusion criteria, and these elements clearly affect the comparison of intra- and postoperative outcomes among them. Despite these clear limitations, our overview allows us to confirm a good feasibility of HTRs use for type 0 and type 1 SMs and, similarly to what happens for "classic" resectoscopic myomectomy, a more difficult procedure for type 2 SMs (although there are reports of type 2 SMs managed in outpatient/office setting). The above reported data suggest that HTR is safe and does not increase the complication rate and postoperative adhesions with respect to resectoscopy, especially for in-training hysteroscopists due to a shorter learning curve. Several studies reported a significant reduction of operative time using HTRs, which may allow a consequent reduction of fluid deficit and avoid its overload. Finally, the medium-term follow-up seems to show good results after HTRs use, especially in terms of patient's satisfaction. The clear disadvantage is the higher cost, considering that the complete treatment of type 2 SMs often requires both HRT and resectoscope in the operating theatre, since HRTs are able to remove the SM once it is completely translated into the uterine cavity.

Nevertheless, HRTs are not so diffused worldwide, therefore data are not enough robust to draw firm conclusion about intrauterine morcellation of SMs, even due to important differences in the design of available studies. In particular, future randomized controlled trials with large cohorts and long-term follow-up with an adequate statistical power should investigate the efficacy of HRTs with respect to "classic" resectoscopic myomectomy, taking into account a possible subanalysis according to number, size, and type of SMs. In

addition, we solicit accurate Health Technology Assessment in order to clarify the cost-effectiveness and impact of healthcare policy of HRTs, especially in office setting.

Disclosure

The authors alone are responsible for the content and writing of the paper.

Conflicts of Interest

All authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service, or company.

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Review Article

The Role of Hysteroscopy in the Diagnosis and Treatment of Adenomyosis

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Uterine adenomyosis is a common gynecologic disorder in women of reproductive age, characterized by the presence of ectopic endometrial glands and stroma within the myometrium. Dysmenorrhea, abnormal uterine bleeding, chronic pelvic pain, and deep dyspareunia are common symptoms of this pathological condition. However, adenomyosis is often an incidental finding in specimens obtained from hysterectomy or uterine biopsies. The recent evolution of diagnostic imaging techniques, such as transvaginal sonography, hysterosalpingography, and magnetic resonance imaging, has contributed to improving accuracy in the identification of this pathology. Hysteroscopy offers the advantage of direct visualization of the uterine cavity while giving the option of collecting histological biopsy samples under visual control. Hysteroscopy is not a first-line treatment approach for adenomyosis and it represents a viable option only in selected cases of focal or diffuse "superficial" forms. During office hysteroscopy, it is possible to enucleate superficial focal adenomyomas or to evacuate cystic haemorrhagic lesions of less than 1.5 cm in diameter. Instead, resectoscopic treatment is indicated in cases of superficial adenomyotic nodules > 1.5 cm in size and for diffuse superficial adenomyosis. Finally, endometrial ablation may be performed with the additional removal of the underlying myometrium.

1. Introduction

Adenomyosis is defined as the presence of endometrial tissue (glands and stroma) within the myometrium; heterotopic endometrial tissue foci are associated with a variable degree of smooth muscle cell hyperplasia [1]. On the basis of myometrial invasion extension, it can be either *diffuse* or *focal*. In the diffuse type, endometrial glands and/or stroma are extensively intermingled with myometrial muscle fibers with an increase in uterine volume (proportionally correlated with the extent of lesions); focal adenomyosis is generally a single nodular aggregate located in the myometrium, which may have a histologic spectrum from mostly ("adenomyoma") solid to mostly cystic ("adenomyotic cyst") [2, 3].

The incidence rate of adenomyosis, generally defined on the basis of hysterectomy specimens, is extremely variable (ranging between 5% and 70%) mainly because of the lack of widely accepted criteria for histopathological diagnosis [4]. It is usually diagnosed in fertile-age women and possible risk factors appear to be pregnancy and previous operative procedures on the uterus.

The exact mechanisms of how adenomyosis develops are still unknown, but the current trend in thought is that adenomyosis or adenomyoma originate from the deep part of the endometrium that invaginates between the bundles of smooth muscle fibers of the myometrium itself, mainly after uterine traumatic events [5, 6]. Thus, uterine manipulations appear to be a crucial factor predisposing the invasion of

endometrial cells into the myometrium [7]. Instead, for uterine adenomyotic cysts—a cystic structure lined with endometrial tissue and surrounded by myometrial tissue that, in most cases, contains haemorrhagic material—direct proliferation of metaplastic myometrial cells of endometrial tissue is supposed to be a possible pathogenetic mechanism, considering the common embryological origin from the Mullerian ducts of the endometrium and the subjacent myometrium [6, 8].

2. Symptoms

There are no symptoms or physical signs that are specific to adenomyosis. However, the cyclic bleeding of the ectopic endometrium resulting in irritation of surrounding tissue often leads to different nonspecific symptoms, including dysmenorrhea (starting at an early age around the time of menarche in the juvenile forms), abnormal uterine bleeding, chronic pelvic pain, and deep dyspareunia [8]. Dysmenorrhea tends to progressively increase and is resistant to therapy with analgesics or cyclic oral contraceptives.

The causative relationship between adenomyosis and subfertility has not been fully confirmed, and the incidence of subfertility in women with adenomyosis has not been defined [8, 9].

3. Diagnosis

Considering the poor specificity of preoperative clinical-based diagnosis, adenomyosis is often an incidental finding in specimens obtained from hysterectomy or uterine biopsies and/or percutaneous ultrasound-based biopsies. The recent evolution of diagnostic imaging techniques, such as transvaginal sonography (TVS), magnetic resonance imaging (MRI), and hysterosalpingography (HSG), has contributed to improving accuracy in the identification of this pathology, with an increasing number of cases described in adolescents and young adult women with untreatable dysmenorrhea [8, 10].

3.1. TVS. With TVS, an *adenomyomatous nodule* may be suspected when there is an oval, hypoechogenic, or hyperechogenic, noncapsulated area in the myometrial thickness, without the posterior cone of shadow and the hyperechoic margin (typical of uterine myomas), variable in diameter. Moreover, small cystic spaces filled with blood, which are rarely >5 mm, may be present [11]. Generally, colour Doppler sonography reveals rich vascularity, which does not circumscribe the lesion and presents an orthogonal orientation in relation to the endometrium [12, 13].

In rare cases, the lesion maybe be seen as a single cyst, with a diameter ≥ 1 cm, filled with a chocolate-brown-coloured fluid, namely *cystic adenomyosis*. It is considered an extremely rare variant of adenomyosis characterized by the presence of a haemorrhagic cyst resulting from menstrual bleeding in the ectopic endometrial glands [6].

Referring to the *diffuse* form, some sonographic characteristics can be helpful in making a differential diagnosis with uterine fibromyomatosis: increased volume uterus, asymmetry in the thickness of myometrial walls, myometrial linear layers, inhomogeneity, poorly defined endometrial-myometrial interface, and thickening of the subendometrial halo. Furthermore, the colour Doppler image shows typical accentuated vascularization with orthogonal orientation relative to the endometrium. Sometimes, there is a typical "Swiss cheese" appearance, presenting numerous, small, irregular cystic spaces (5–7 mm in diameter) within the myometrium [12, 14].

A TVS may also permit differentiation between surface and deep adenomyosis, which can be used to counsel the patient on the most appropriate therapeutic management: only the superficial variant is amenable to resectoscopic treatment [2, 14].

The application of 3D TVS to adenomyosis is a recent development and few articles have been published. As extensively described by Exacoustos et al., 3D ultrasound signs of adenomyosis are based on the evaluation of the junctional zone (JZ) (i.e., the inner myometrial layer immediately underlying the endometrium, composed of higher cellular density and a higher nuclear area compared to the outer myometrium) on the acquired volume of the uterus in order to obtain the coronal view; the JZ appears as a hypoechoic zone around the endometrium [15, 16].

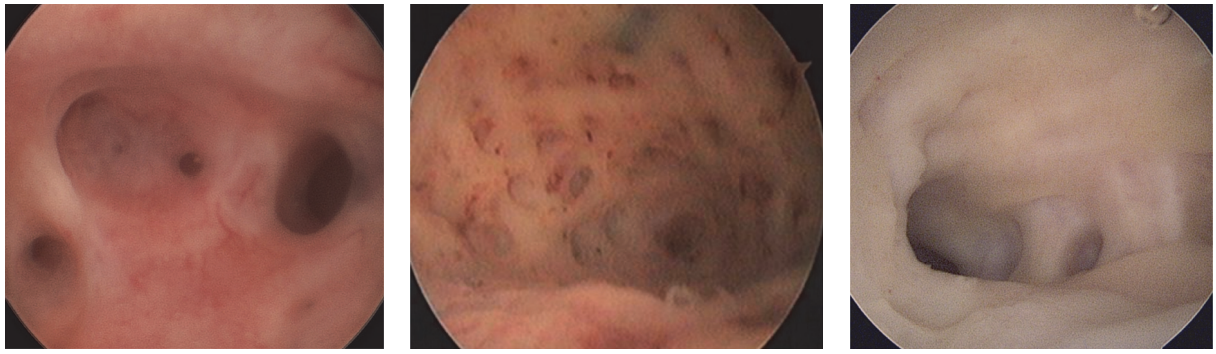
Any irregularity in the JZ can be described in each location of the uterus; it could be visible and regular or, on the contrary, irregular, interrupted, not visible, or not assessable [15, 17]. For morphological descriptions of the JZ, objective parameters have been proposed, based on the MRI evaluation technique: thickness, regularity, and interruption of JZ [18]. In this way, 3D TVS, with the reconstruction of uterine anatomy in the coronal plane, provides a new view of the JZ, previously only well evaluated with MRI.

3.2. MRI. The JZ is easily seen with MRI, as a low signal intensity zone. The presence of adenomyosis is related to uncoordinated proliferation of these inner myometrial cells, resulting in focal or diffuse JZ hyperplasia: it can be seen on T2-weighted MRI as diffuse or focal thickening of the JZ.

As previously reported, the evaluation of the JZ in an MRI exam is based on three main parameters: thickness, regularity, and interruption of JZ.

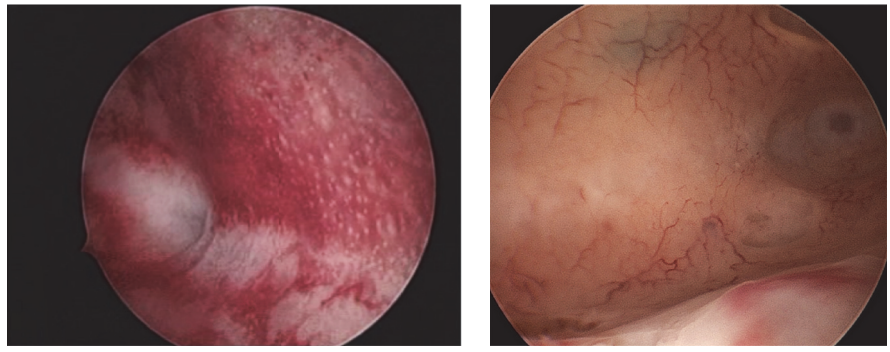
Thickness must be measured at the thinnest (JZmin) and thickest (JZmax) part, at the anterior and posterior wall in the sagittal slices. Diffuse adenomyosis is diagnosed given a JZmax of 15 mm. If the JZ is 12–15 mm in thickness, a diagnosis of adenomyosis arises only in the presence of additional criteria (such as loss of smooth appearance of the JZ, poorly circumscribed foci within the myometrium with high or low intensity) [14, 19]. In cases of focal adenomyosis, T2-weighted sequences show a decreased subendometrial signal intensity (consistent with the presence of necrotic tissue) with blurred margins surrounding the lesion [14].

An additional proposed parameter is the difference between JZmax and JZmin (JZdif), calculated for the anterior or posterior border. Any eventual JZ irregularity can be measured as JZdif, representing an additional characteristic of adenomyosis [20].



(a) (b) (c)

Figure 1: Hysteroscopic view of irregular endometrial mucosa due to the presence of tiny openings on the endometrial surface. These images suggest the hypothesis of adenomyosis.



(a) (b)

Figure 2: Hysteroscopic image suggestive of adenomyosis under hysteroscopic examination and then confirmed at histological exam after hysterectomy. (a) The typical endometrial "Strawberry" pattern with signs of hyperemia and areas appearing bright red harbouring white central dots. Fundal, irregular vascularization, small subendometrial haemorrhagic cyst.

Diagnostic MRI cluster of cystic adenomyosis relies on the detection of a complex cystic lesion that is usually located within the myometrium, with hyperintense T1-w and intermediate to hyperintense T2-w signal contents suggesting haemorrhagic and/or proteinaceous products. In addition, the presence of surrounding T2-hypointense tissue is indicative of reactive myometrial hypertrophy, and/or thin rim cystic wall may show hypointense T1-w and T2-w signal, suggestive of the presence of hemosiderin due to endometrial sloughing [21].

3.3. HSG. Occasionally, HSG is of diagnostic value, identifying one or more of the following features: "*lollipop-like*" diverticula (direct sign), dilated tubes (indirect sign), and prominent spicules (indirect sign).

3.4. Hysteroscopy. Hysteroscopy offers the advantage of direct visualization of the uterine cavity while giving the option of collecting histological biopsy samples under visual control [22, 23].

However, diagnostic hysteroscopy cannot establish a definitive diagnosis of adenomyosis, considering that its field of vision is restricted to the endometrial surface layer. The following aspects are generally indicative of the pathological condition:

(i) irregular endometrium with tiny openings seen on the endometrial surface (Figure 1);

(ii) pronounced hypervascularization;

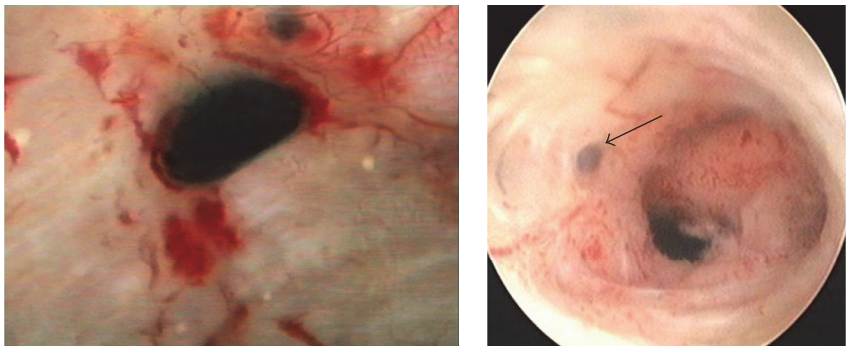
(iii) an endometrial "strawberry" pattern (Figure 2(a));

(iv) fibrous cystic appearance of intrauterine lesions (following 3–5 episodes of intramyometrial haemorrhage) (Figure 2(b));

(v) haemorrhagic cystic lesions assuming a dark blue or chocolate brown appearance (Figure 3) [24].

In patients with adenomyosis, hysteroscopy reveals an irregular endometrial vascular distribution pattern, both during the proliferative and secretory phase. Moreover, it allows obtaining biopsy samples from the endometrium and underlying myometrium using mechanical instruments (biopsy or grasping forceps, scissors) or bipolar electrodes [24].

The traditional technique to assess the extent of adenomyosis infiltration is biopsy sampling performed using a resectoscope with a diathermic loop, to perform the resection of the endomyometrial layer concerned. In order to obtain an



(a) (b)

Figure 3: Hysteroscopic images of small haemorrhagic foci assuming a chocolate brown colour, suggestive of adenomyosis (diagnosis was confirmed at histological exam on target-eye biopsies).

adequate biopsy with this approach, it is first of all necessary to have a specimen including both the endometrium and the underlying myometrium layer and then take a second biopsy deeper into the dent left behind by the first, including only myometrial tissue [15, 16]. Generally, on resectoscopic biopsy sampling, the following three clues can be strongly suggestive of adenomyosis: (1) irregular subendometrial myometrium (spiral and/or fibrotic); (2) contortion of normal myometrial architecture noticeable during resection; (3) presence of intramural endometriomas.

Recently, Gordts et al. described the use of a new gliding system, the *Trophy° Hysteroscope (Karl Storz, Germany)* that offers the possibility of changing from a diagnostic 2.9-mm hysteroscope to an operative 4.4-mm scope without the need to remove the hysteroscope [8]. 5-Fr instruments are used for dissection/coagulation through the operative channel. With the application of a new device, the *Utero-Spirotome*, it is possible to have "direct and frontal" tissue harvest, allowing the biopsy of endomyometrial layers.

Spirotome operates with two devices: the receiving needle with a cutting helix at the distal end and a cutting cannula as an outer sheet; the correct direction and position of the helix point must be under continuous ultrasonographic imaging and hysteroscopic control. In this way, the Spirotome can be directed towards any intramural localized lesion such as cystic adenomyosis, thus creating a visible hysteroscopic channel that allows access to the cystic cavity. Thanks to this device, the hysteroscopy can offer an alternative access to cystic adenomyosis, producing minimal tissue damage [8].

4. Treatment

Considering the relevant technical progress seen in recent years and the increasing rate of preoperative diagnosis of adenomyosis, it is currently possible to perform a "tailored" treatment for any patient, based on the several available medical and surgical options.

The factors to be taken into consideration in order to choose the correct therapeutic strategy are patient age, desire for a future pregnancy, symptoms, and coexisting pelvic diseases.

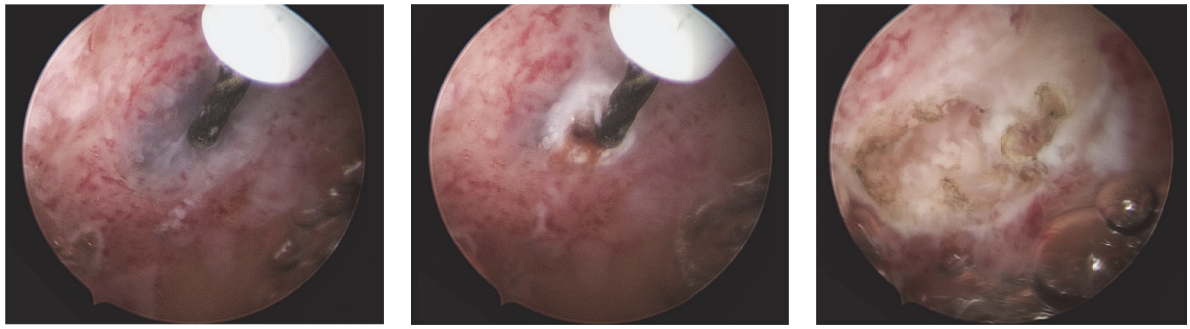
Medical approach to adenomyosis disease is based on its hormone dependent nature and on its similarities to endometriosis: in this sense, effective therapies for endometriosis can potentially be adequate for adenomyosis. Generally used medical treatments for adenomyosis include gonadotropin-releasing hormone agonists (GnRH-a), levonorgestrel-releasing intrauterine device (LNG-IUD), oral contraceptive combined pill, progestogens, and danazol [25–27]. The principal limit of these medical options is that they induce regression but not eradication of the pathology, with symptom recurrence after drug discontinuation.

Regarding surgical treatment, a critical question is whether to remove or preserve the uterus. Hysterectomy remains the standard treatment for symptomatic adenomyosis for patients who do not desire a future pregnancy and who accept the operation. Hysterectomy can be performed by laparoscopy or laparotomy or vaginally, based on uterine size, parity, and surgeon's experience.

In the cases where women decline hysterectomy or wish to pursue future pregnancy and the surgical approach is chosen, it is necessary to accurately define the characteristics of the adenomyosis and consequently the "way" to access the lesions for conservative treatment. The concept of conservative "uterine-sparing" surgery (either performed by laparoscopy/laparotomy or hysteroscopy) for adenomyosis is increasing as fertility preservation and quality-of-life improvement can be achieved in this group of patients [28].

The surgical technique for excision of focal adenomyosis, by laparotomy or laparoscopy, is similar to myomectomy in many technical aspects, although it can be more difficult because adenomyosis generally lacks a cleavage plane. When the adenomyotic lesion can be clearly preoperatively defined (by TVS or MRI) laparoscopy is a feasible technique, and laparoscopic suturing presents no more difficulty compared with suturing after myomectomy for a skilled surgeon [29].

Diffuse adenomyosis typically involves the myometrium in an irregular and massive way, characterized by lesions with unclear borders, so much so that complete excision of



(a) (b) (c)

Figure 4: Evacuation of hypothesized superficial adenomyotic cysts with a 5-Fr bipolar electrode (KARL STORZ, Germany). Panoramic image of the small cystic lesion (a). Incision and drainage of the cystic lesion (b-c).

adenomyotic tissue is not possible, with obligate loss of healthy myometrium. In these cases, the laparotomic approach should be chosen, because digital palpation of the uterus is necessary to delineate the involved areas, limiting the excision of healthy myometrium. Preservation of at least 1–1.5 cm of myometrial thickness is needed for uterine reconstruction, which can be particularly challenging after an extensive excision. Multiple layers of interrupted sutures are preferred for good repair and better obstetrical outcome [30].

Finally, preliminary results of "nonexcisional" conservative techniques are described in recent literature, such as laparoscopic electrocoagulation of the myometrium, laparoscopic uterine artery ligation, ablation of focal adenomyosis with high frequency ultrasound (HIFU), alcohol instillation under ultrasound guidance for the treatment of cystic adenomyosis, radiofrequency ablation of focal adenomyosis, and balloon thermoablation for diffuse adenomyosis [31].

Nevertheless, data supporting these types of intervention are still suboptimal, and prospective, comparative studies are needed.

5. Hysteroscopic Treatment

Hysteroscopy is not a first-line treatment modality for women with adenomyosis and represents a viable option only in select cases of the focal or diffuse superficial subtype.

5.1. Office Hysteroscopy. It is possible to enucleate superficial focal adenomyomas or to evacuate cystic haemorrhagic lesions of less than 1.5 cm in diameter, using mechanical instruments and/or bipolar electrodes (Figure 4). This treatment is feasible only when the lesions are directly recognizable at hysteroscopy as they bulge into the endometrial cavity, thus favouring a minimally invasive dissection (Figure 5).

The traditional technique adopted in the ambulatory setting is the same used for enucleation of submucosal myomas with an intramural component, even though the procedure involves a considerable element of precautionary exploration due to the lack of a distinct cleavage plane required for adequate identification of healthy myometrial tissue [8, 22].

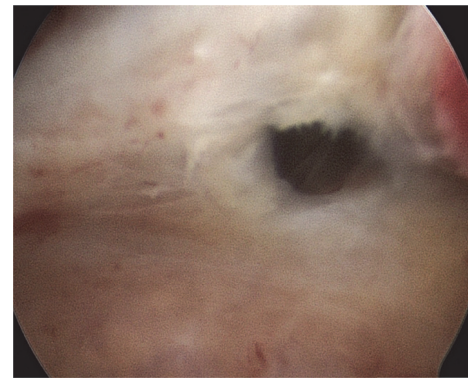


Figure 5: Hysteroscopic image of cystic adenomyotic lesion at the fundus of uterus affected by diffuse adenomyosis (diagnosis was confirmed at histological exam on target-eye biopsies), after incision with bipolar electrodes.

Moreover, for cystic lesions localized deeper in the intramural portion (defined as *subtype A* by Brosens et al. in a recent review on the topic) [10], the Spirotome is a very useful innovation; under ultrasound guidance, access is gained to intramural cystic lesions without visible intracavitary components. The device creates a channel and provides hysteroscopic access to the cystic structure. Treatment by resection or bipolar coagulation can then be performed [8].

5.2. Resectoscopic Treatment. This is indicated in cases of superficial adenomyotic nodules > 1.5 cm in size and for diffuse superficial adenomyosis. Endometrial ablation may be performed with the additional removal of the underlying myometrium *(endomyometrectomy)* mainly in women not desiring future pregnancy.

Deep diffuse adenomyosis, instead, is not manageable with the hysteroscopic approach [32]. Some authors have demonstrated that, given a deep adenomyosis, resectoscopic treatment not only fails to reduce symptoms, but may even have adverse effects in that it masks the onset of deep adenomyosis developing below the endomyometrial

scar tissue, which may consecutively be prone to malignant transformation.

To treat *focal* adenomyosis, the technique of adenomyomectomy has yet to be exhaustively defined. Tissue protruding into the uterine cavity is incised, evacuated, and resected (by slicing) using a resectoscope with a cutting loop. In cases of deeply implanted lesions, the nodule may first be mobilized using various techniques that cause it to migrate into the uterine cavity. These techniques have already been described for the treatment of a submucosal myoma with an intramural component, which is serially resected with a cutting loop until it can be completely removed. The surgical procedure is completed by coagulating the implantation base of the lesion.

The goal of surgery is to remove all adenomyotic tissue without damage to healthy surrounding myometrial fibers. However, the lack of a distinct cleavage plane indicating the normal myometrial tissue can make the procedure quite challenging [33, 34].

Superficial diffuse adenomyosis may be treated with endomyometrial ablation (endomyometrectomy). The technique differs from the classical method of endometrial ablation as resection is not limited to the endometrium and the first 2-3 mm of myometrium; rather, the operator proceeds with continued slicing of the myometrial layer below, until healthy myometrium is visualized, and concludes the procedure by coagulation of endometrial residues. The procedure is accomplished using 3-mm or 5-mm straight loops for ablation of the fundus and cornual recesses, as well as classic cutting loops for ablation of uterine walls.

The level of intramural extension of pathology is correlated with the technical difficulty and risks of the procedure. In the case of persistence and/or recurrence of disease, a second-stage surgical procedure may be performed.

However, meticulous care must be paid to the thickness of the myometrium between the outer margin of adenomyosis and the uterine serous surface, evaluated by ultrasound. Endomyometrectomy may give rise to dissemination and proliferation of ectopic endometrial cells, promoting progression of the pathology and "de novo" adenomyosis.

Adjunct to surgery, or as an alternative option, local medical therapy by application of a levonorgestrel-releasing IUD may be chosen. The continuous controlled release of LNG, directly at uterine mucosal level, may induce regression of adenomyotic lesions along with relief of pain symptoms [35].

6. Conclusions

Hysteroscopy has revolutionized the way to approach adenomyosis, in terms of both diagnosis and therapy.

Traditionally, adenomyosis has been diagnosed by the pathologist in hysterectomy specimens. Thanks to the advent of high definition noninvasive methods (TVS and MRI) diagnosis comes earlier and on a large scale. Moreover, the possibility of presurgical diagnosis allows an individualized therapeutic approach based on the individual needs of the patient.

The introduction and successive diffusion of office hysteroscopy has greatly enriched the diagnostic phase of this pathology, adding all the information regarding the endometrial surface of the affected uteri. Furthermore, hysteroscopy allows obtaining target-eye biopsies (also guided by sonographic control), which can definitively confirm the endoscopic diagnosis.

Hysterectomy remains the standard treatment for symptomatic adenomyosis if fertility is not an issue. In the cases of women who refuse hysterectomy or desire a future pregnancy, the decision is more complex. The use of medical therapies is mainly based on the observation that the disease is hormone dependent and on the similarities to endometriosis. Regarding surgery, the approach to focal deep adenomyosis by laparoscopy or laparotomy reflects the similarity of this pathology to a leiomyoma, although the technique for adenomyomectomy can be more challenging.

Finally, operative hysteroscopy (either with miniaturized instruments or standard resectoscope) may be indicated in cases of superficial adenomyotic nodules and for diffuse superficial adenomyosis.

Conservative uterine-sparing treatments of adenomyosis appear to be feasible and efficacious. An improvement of dysmenorrhea and menorrhagia is achieved in more than 81% and 50% of the patients, respectively [31]. On the other hand, data supporting this type of intervention for improving pregnancy outcome are still suboptimal and need to be confirmed by well-conducted studies, where many potential confounding factors of infertility should be adequately assessed [29, 36, 37].

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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