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Special Issue Editor in Chief: Andrea Tinelli
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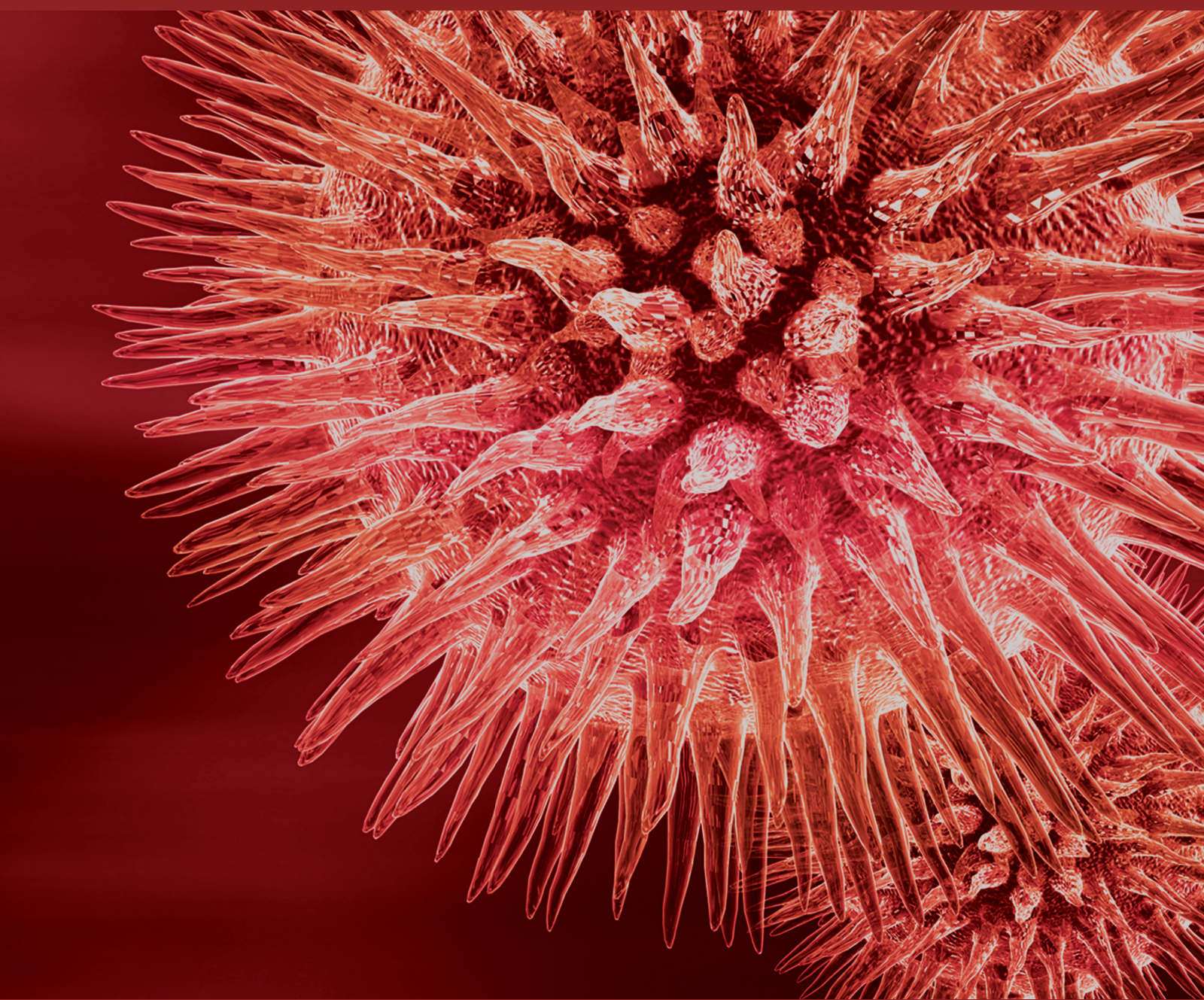

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Editorial

Uterine Fibroids: From Molecular Oncology to Reproduction

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Smooth muscle uterine tumors include a large group of neoplasms representing the entire spectrum, from benign to malignant cancers. This includes benign fibroids, STUMPs (smooth muscle tumors of uncertain malignant potential), and leiomyosarcomas (LMS). Uterine fibroids, also known as myomas or leiomyomas, are the most common benign tumors of the genital organs of women of childbearing age. Literature data show that up to 77% of women have fibroids, either depending on the study population or by diagnostic techniques applied to myoma detecting.

Symptomatic fibroids account for approximately over 200,000 hysterectomies and 50,000 myomectomies annually in the United States and may cause significant morbidity, including abnormal uterine bleeding, infertility, or bulk symptoms causing pelvic discomfort. Fibroids have a major impact on fertility, with an overall significant adverse effect for fibroids on implantation rate and spontaneous abortion rates when compared with infertile women without fibroids. Impaired peristalsis, inflammatory response and physical deformity of the uterine cavity by fibroids may all play an overall role in reducing fertility outcomes. Moreover, fibroids are associated with abortion and adverse obstetric outcomes, abnormal placentation, placental abruption, premature rupture of membranes, postpartum hemorrhage, and preterm birth. Fibroids are more common in women over 40 years, when fibroids and infertility are more frequent and prevalent, which increases the risk of this association and of associated complications.

Because of the wide-spread nature of this disease, uterine fibroids are the number one pathologic cause of surgery in gynecological patients. In addition, this common female pathology has a negative impact on wellbeing, with a significant female morbidity and impairment of quality of life. According to the literature, 40-60% of all hysterectomies are scheduled for symptomatic fibroids, as the most common worldwide indication.

Fibroids consist mainly of smooth muscle cells with different amounts of fibrous tissue surrounded by a neurofibrovascular network, the myoma pseudocapsule, which enables their enucleation and enhances myometrial healing. Because of the wide-spread nature of this disease, clinical interventions and costs associated with uterine myomas are constantly growing. For this reason, the interest and research in different myoma aspects including transcription factors and gene targets involved in myoma development and new pharmacological and surgical treatments have grown exponentially in the last several years.

Myomectomy is not a risk-free operation, since the surgical procedure can cause mechanical infertility and can be associated with infection, injury to adjacent tissues, and hemorrhage. There are robust surgical outcome data supporting the use of a minimally invasive surgery (MIS) such as laparoscopy and hysteroscopy over laparotomy. Perioperative outcomes and return to normal activity are significantly better with MIS.

Differentiating between leiomyoma and leiomyosarcoma presurgically can be difficult, particularly in premenopausal patients. Frequently, myoma at rapid growth can be confused and misdiagnosed with a LMS in women over 40 years of age. This malign neoplasm is a rare, aggressive cancer of the uterine muscle cells, clinically difficult to distinguish from benign leiomyomas. The annual incidence of leiomyosarcoma (LMS) is less than two women per 100 000 based on the population-based Surveillance, Epidemiology and End Results (SEER) database from the USA National Cancer Institute, so it is a rare tumor (3 to 7 per 100,000 in the USA population). The incidence of LMS increases with age and is diagnosed usually after menopause, around 60 years of age. It is more common in the African American race and after prolonged use of tamoxifen of over 5 years. LMS has a poor prognosis even in early-stage disease due to an early hematogenous spread. Pritts and colleagues estimated in 2015 the likelihood of finding a leiomyosarcoma in general population. The estimated rate of leiomyosarcoma was 0.51 per 1000 procedures or approximately one in 2000. In assessment by meta-analysis, there was a substantially lower estimate of 0.12 leiomyosarcomas per 1000 procedures or approximately one leiomyosarcoma per 8300 surgeries. Literature recently reviewed the risk of occult leiomyosarcomas found at surgery for presumed benign fibroids, since leiomyosarcomas are most commonly diagnosed following myomectomy or hysterectomy for presumed leiomyomas. Moreover, there is no pelvic imaging modality that can reliably differentiate between benign leiomyomas and LMS. In addition, there are currently no validated clinical or radiographic criteria to differentiate a leiomyoma from a LMS, as the final diagnosis made histopathologically after hysterectomy or myomectomy.

Our special issue, which had opened for 3 months in the end of 2017, focused on uterine fibroids, focusing on their impact on female wellbeing and treatment. An article of H. S. Saleh et al. investigated the impact of fibroid on obstetric outcome in pregnancy, by a prospective observational study in Egypt, on 64 pregnant patients with >2 cm fibroids. Patients were followed during antenatal period clinically and scanned by ultrasound, which was performed at starting of pregnancy and during subsequent visits, to assess the change in the size of the fibroid and other obstetric complications. Authors recorded increased size of fibroids, complications during pregnancy, labor, delivery, and changes in mode of delivery. They concluded that while most fibroids in pregnancy are asymptomatic, pregnant patients who have fibroids have a higher incidence of complications throughout antepartum, intrapartum, and postpartum period. Therefore, they should be carefully screened in the antenatal period through regular follow-up.

Another study of A. Tinelli et al. investigated the difference of myoma pesudocapsule thickness measured in 200 submucous, intramural, and subserous fibroids by histology and ultrasound and evaluated its possible correlation with fertility impairment caused by fibroids. The thickness of the pseudocapsule was greater for the submucosal myomas, compared, respectively, to the intramural and subserous, suggesting a potential role in fertility or in myometrial healing.

The investigation of I. Mazzon et al. analyzed which variables influenced the completion of a cold loop hysteroscopic myomectomy in a one-step procedure, by a retrospective cohort study of 1434 operations consecutively performed and 1690 removed fibroids. The multivariate analysis showed that the size, the fibroids' number, and the age of patients were significantly correlated to the risk of a multiple-step procedure. No correlation was revealed with the fibroid grade, parity, and the use of presurgical GnRH-agonist therapy. Authors concluded that in case of multiple fibroids the intramural development of submucous myomas did not influence the completion of cold loop hysteroscopic myomectomy in a one-step procedure. The size of myomas and the age of patients were significantly correlated with the need to complete the myomectomy in a multiple-step procedure.

J.-J. Li et al. reviewed the management of adenomyosis in women wishing to improve or preserve fertility, starting form adenomyosis pathogenesis, clinical presentation, diagnosis by instrumental and histological detection, and pharmacological and surgical therapy, evaluating the impact of patients' fertility.

Finally, T. D. Lewis and colleagues published a comprehensive review of the pharmacologic management of uterine leiomyoma, evaluating the effect of nonhormonal and hormonal treatments, aromatase inhibitors, gonadotropin-releasing hormone analogs, and selective progesterone receptor modulators on fibroids.

In conclusion, we expect that this special issue provides a valuable update on the scientific progress of uterine research, notably adding insight and future direction on scientific research and fibroid clinical practice.

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Research Article

Submucous Fibroids, Fertility, and Possible Correlation to Pseudocapsule Thickness in Reproductive Surgery

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Background and Objectives. Fibroids are related to infertility. Fibroid pseudocapsule is a neurovascular bundle surrounding leiomyomas rich of neurofibers involved in myometrial biology. Authors evaluated, by a case-control study, the fibroid pseudocapsule (FP) thickness by ultrasound (US) and the histological measurements, according to uterine location of fibroids. *Methods*. 137 consecutive patients undergoing hysterectomy for uterine myomas were enrolled and 200 myomas were evaluated. Before surgery, patients underwent an ultrasound (US) investigation to evaluate the number, the size, and the location of fibroids. After surgery, myoma-pseudocapsule-myometrium specimens were measured and evaluated by a single expert pathologist. Both US and histological data were collected and statistically analyzed. *Results*. Our results confirm the relevant difference of FP thickness, particularly represented under the endometrium for submucous LMs. FPs near the endometrial cavity were considerably thicker than those of both intramural fibroids and subserous fibroids measured by US (P=0.0001) and histology (P=0.0001). A clear cut-off measurement at 2 mm (P=0.0001) was found between endometrial FPs and all other FPs for either US or histology measurements. *Conclusion*. The thickness of FP is considerably higher near the endometrial cavity when compared to those of both intramural and subserous LMs, suggesting a potential role either in fertility or in myometrial healing.

1. Introduction

Uterine fibroids or leiomyomas (LMs) are the most common worldwide indication for hysterectomy [1, 2]. Although mostly of women with fibroids are asymptomatic, LMs can cause abnormal uterine bleeding, pelvic pain, and reproductive dysfunction [1]. It is difficult to assess a correct uterine LMs incidence as it increases with ageing. They may occur in more than 30% of patients of 40-60 years [3]. Nowadays, uterine LMs represent not only a problem for the women health, but also a heavy economic burden. It has been estimated that the American social costs for uterine LMs, in terms of costs of care, adverse obstetric outcomes, and work-hours lost, are higher than that ovarian, breast, and colon

cancer [4]. In the last decade, several pharmacological [5] and surgical treatments have been proposed for a conservative management of uterine LMs [6, 7].

In order to preserve fertility, a conservative treatment should be proposed to women wishing pregnancies, especially in those younger patients who want to undergo assisted reproductive techniques (ART). There is a general agreement that submucosal LMs negatively affect fertility, when compared to women without fibroids. A recent review reported that intramural LMs above a certain size (>4 cm), even without cavity distortion, may also negatively influence fertility and the presence of subserosal LMs has little or no effect on fertility [8].

Nevertheless, some studies reported conflicting results and much of the data shows no differences in outcomes no matter the size of fibroids. Vimercati et al. [9] affirmed that patients with fibroids >4 cm required an increased number of cycles to obtain an ongoing pregnancy, compared with the other groups. On the contrary, Oliveira et al. [10] concluded that patients with subserosal or intramural fibroids < 4 cm had IVF-ICSI outcomes (pregnancy, implantation, and abortion rates) similar to those of controls and women with intramural fibroids > 4.0 cm had lower pregnancy rates than patients with intramural fibroids ≤ 4.0 cm of diameter.

Yan et al. [11] showed that women with intramural fibroids with the largest diameter < 2.85 cm or the sum of reported diameters < 2.95 cm had a significantly higher delivery rate than patients with larger fibroids. A significant negative effect on delivery rate was noted when intramural fibroids with the largest diameter greater than 2.85 cm were considered, compared with matched controls without fibroids. Although noncavity-distorting fibroids do not affect IVF/ICSI outcomes, intramural fibroids greater than 2.85 cm in size significantly impair the delivery rate of patients undergoing IVF/ICSI. On the other side, Savarelos et al. [12] reported that women with intracavitary distortion and undergoing myomectomy significantly reduced their midtrimester miscarriage rates in subsequent pregnancies from 21.7 to 0% (P< 0.01). This result have been translated to an increase in the live birth rate from 23.3 to 52.0% (P< 0.05). Conversely, Yarali et al. [13] affirmed that the implantation and clinical pregnancy rates were similar on intramural and subserous fibroids (that did not distorted the uterine cavity). Horcajadas et al. [14] concluded their study with no correlation between implantation and miscarriage with leiomyoma number and size, although the focus of the study is in the gene expression and not on a comparative study between the position, size, and number of fibroids.

Trying to understand the correlation between LMs and fertility, some authors deeply studied the LMs anatomical and biological structure, in order to develop even more conservative and effective treatments [15, 16]. From the LMs anatomy studies, the neuroendocrine-biological role of the fibroid pseudocapsule (FP), a sort of neurovascular bundle surrounding LM, on myometrial physiology emerged [17]. Several studies have highlighted a new endocrine function of such structure, which may have a potential role in the uterine healing and fertility, especially after myomectomy [18–24]. Recently, a nontumoral origin of FP has been speculated, but rather a protective structure from the healthy myometrial tissue that could enhance regenerative mechanisms [25].

The FP is a well-known anatomical entity, which can be sonographically [17, 25] and histologically evaluated [26]. In a previous preliminary report [27], authors examined the pseudocapsule thickness according to uterine location of LMs, detecting a high correspondence between ultrasound (US) and the histological measurement. Nevertheless, the FP was considerably thicker over the submucous myomas when compared to those of both intramural and subserous LMs, suggesting a potential role in healing mechanism. The limits of such investigation involved a limited number of patients. Therefore, the aim of such prospective case-control study with single surgeon was to validate the results raised in the previous report and to assess the repeatability of the measurement techniques in a large cohort of patients.

2. Material and Methods

From 2009 to 2015, authors conducted a prospective single centre study conducted in Italian affiliated University Hospital, in a cohort of patients affected by fibroids and scheduled for hysterectomy. All selected patients consented to take part in research, as well as be operated. The study design was approved by the IRB. All procedures were in accordance with the guidelines of the Helsinki Declaration on human experimentation. All enrolled patients complained symptoms related to fibroids, such as heavy menstrual bleeding and pelvic pain. The surgical treatment was clinically indicated and the patient care was not altered by participation in this study.

A written, informed, and signed consent for hysterectomy was signed from all patients. Cases of endometrial hyperplasia, uterine polyps, cervical intraepithelial neoplasia, uterine or cervical cancer, confirmed or suspected primary adnexal pathology, adenomyoma, or adenomyosis were excluded from this study.

Fibroids were excluded from statistical analysis if they had been mapped as intraligamentary and/or in the isthmic-cervical region, as well as pedunculated.

Before surgery, patients underwent an ultrasound investigation in the first 10 days of the menstrual cycle to evaluate the number, the size, and the location of fibroids according to the LMs subclassification system of International Federation of Gynecology and Obstetrics (FIGO), with the following classification: Group 1: FIGO Classes 1&2, Group 2: FIGO Classes 3&4, and Group 3: FIGO Classes 5&6 [25].

Moreover, the pseudocapsule thickness (the white ring surrounding the myoma) was measured for each myomas following the methods described in the previous report [26].

The US examination and measurements were performed by a single US-expert (A.T.). The following US systems, a Logic 7 Pro US system (GE-Kretz, Zipf, Austria) or a Voluson 730 US system (GE-Kretz, Zipf, Austria) equipped with a 3.8 to 5.2 MHz transvaginal transducer, were used. Both machines were settled by the producer Industries with a medium-level quality, by a standard US setting of Doppler and gray scale.

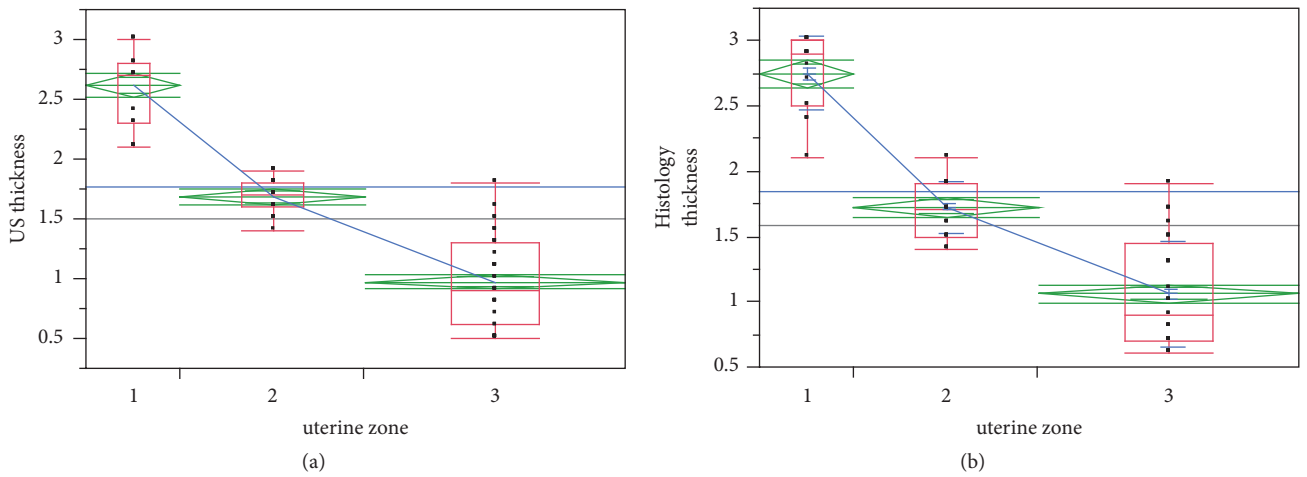

Figure 1: (a) The myometrial fovea after enucleation of the myoma; (b) the pseudocapsule with white fibro-connective bridges highlighted during hysteroscopic myomectomy.

The hysterectomies were performed both in laparoscopic or laparotomic setting at the first ten days of menstrual cycle. After surgery, myoma-pseudocapsule-myometrium specimens were measured and evaluated by a single expert pathologist (M.P.), blinded for patients' data. Pathologic analysis was carried out by the same methodology described in the previous report [26]. Afterwards both US and histological data were collected and send for statistical analysis to a member of this international research team, then all results were analyzed, and manuscript was drafted by three members of this team.

3. Statistical Analysis

FP measurements have been tested for normal distribution using Q-Q plots. Both LM thicknesses, measured by US and histology, were analyzed by the one-way ANOVA test. P value <0.05 was considered as statistically significant. By extending the ANOVA method, we used each pair of Student's T test (<0.05, all pairs Tukey-Kramer test (<0.05) comparison with Best Hsus MCB (<0.05) and Dunnett's (<0.05). Exploratory analysis was performed with partition with three splits, because no prior model existed. Pearson correlation was employed to find whether positive correlation exists between the two measurements, because data are normally distributed (Q-Q plots not seen). Area under the curve was performed with ROC curves. Analyses were conduct with the Statistical Package JMP 9 (SAS) and SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

4. Results

One hundred and thirty-seven consecutive patients undergoing hysterectomy for LMs were enrolled in this study. Normal distribution was observed in the tree FIGO classification groups. The total enucleated LMs were 200: 62 fibroids in FIGO Classes 1&2, 73 in FIGO Classes 2&3, and 65 in FIGO Classes 5&6.

FPs near the endometrial cavity were considerably (P=0.0001) thicker than those of both intramural and subserous LMs measured by US (2.62 ± 0.31 versus 1.68 ± 0.13 and 0.97±0.36 mm) and histology (2.75±0.27 versus 1.72±0.2 and 1.06 ± 0.4 mm), respectively.

Significant difference was observed between the three groups, for both measurements, using all tests mentioned above (Figures 1(a) and 1(b)).

On exploratory analysis, a clear cut-off measurement at 2 mm (P=0.0001) was found between near the endometrium FPs and all other FPs for either US or histology measurements. Area under the curve was 0.949 for US and 0.953 for histology for endometrial cavity fibroids (Figure 2).

Correlation between ultrasound and histology measurements was near 1, indicating that ultrasound and histology measurements are positively correlated (0.954 P=0.000) (Pearson correlation).

5. Discussion

Authors have found that the FP thickness was significantly different according to LMs uterine position. The FP of the submucous LMs appears considerably thicker in comparison than those of both intramural and subserous LMs. These features of FP depending their localization were observed both in presurgical US and in the histological examinations and US and histological measurements were highly correlated. A major strength of this study compared to the previous one [26] is the large cohort of involved patients.

Submucosal fibroids have a statistically significant negative effect on clinical pregnancy rates as reported by a meta-analysis of 13 studies [22]; the study also showed a lesser extent of intramural fibroids on clinical pregnancy rates. About delivery rates, submucosal and intramural fibroids showed a negative impact. On the contrary, subserosal myomas did not showed any effect on clinical pregnancy rates and delivery rates.

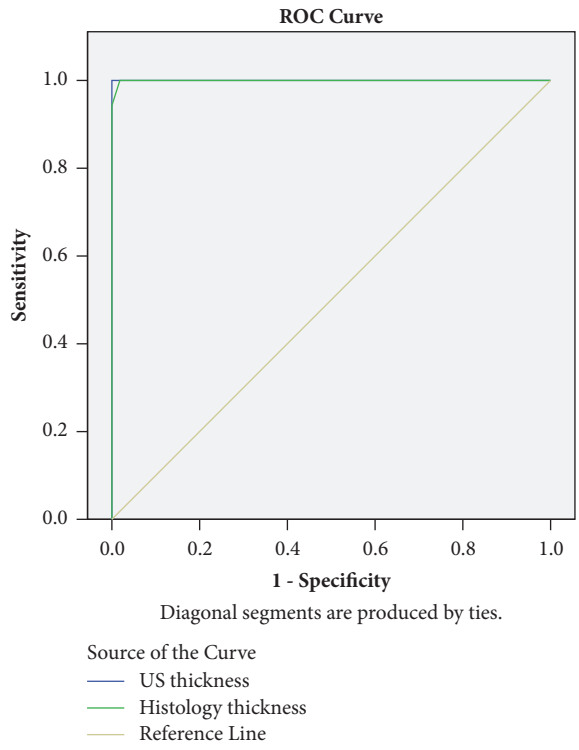

Figure 2: Area under the curve for US measurement (0.949) and histology measurements (0.953) for pseudocapsule thickness from fibroids of endometrial cavity location. Values are near 1, thus indicating that this test is of high accuracy for pseudocapsule measurements of endometrial cavity fibroids.

A meta-analysis of Pritts et al. [23] showed that fibroids are generally linked to a statistically significant decrease in fertility, regarding clinical pregnancy and birth rates and, simultaneously, an increase in miscarriage rates. The submucosal fibroids have the greatest negative statistical correlation on clinical pregnancy rates, so intramural fibroids resulted in significantly lower birth rates and higher miscarriage rates.

Pritts et al. [23] concluded that both patients with submucosal and intramural fibroids have poorer reproductive outcomes compared to patients without fibroids.

Thus, submucous and intramural LMs are more involved for sterility and infertility cases due to alteration of uterine cavity and contractility, while subserosal fibroids do not seem to generate any obvious fertility issue.

These surgical conclusions conflicted with studies focusing on endometrial receptivity in uteri with submucosal fibroids, showing surgical removal of intramural fibroids with no improvement in outcomes. Rackow et al. [28] reported that endometrial receptivity markers significantly decrease in submucosal fibroids, while the same is evident for intramural fibroids [29], especially for the HOXA10 gene. After intramural myomectomies a statistically significant increase was observed by Unlu et al. [30] in these receptivity markers, but unfortunately they did not observe such an effect in the submucosal myomectomies. Overall, only these two studies exist in the endometrial receptivity and myomectomy. Although evidence is still minimal, we assume that one factor of improved implantation rates after removal of intramural and submucosal fibroids is the improvement of implantation profile. Although, preservation of pseudocapsule achieves no early postoperative complications and good fertility rates [31], new studies need to be performed in the role of fibroid pseudocapsule preservation and the implantation markers.

From the other side, many other theories have been developed until now for the improvement of fertility rates after submucosal myomectomy. Horne et al. [32] reviewed the theory, as the mechanical distortion of the endometrial cavity, the disruption of the junctional zone within the myometrial layer, the altered vasculature due to the abnormal expression of angiogenic factors, the inflammation mediated changes in the endometrium, and, as lastly new, the alteration of endometrial receptivity factors.

In view of the above surgical evidences, we could correlate the greater thickness of the FP in the submucous and then in the intramural LMs. Among the possible theories which have been proposed in order to explain how fibroids may impair fertility [8], although we do not have a clear explanation of why there is an increase in thickness in LMs in submucous and intramural LMs, we must consider this evidence and further study it.

Our theories formulated on pseudocapsule thickness potential impact in fertility for future investigation consider mechanical reasons and differences in genetic expression components.

The pseudocapsule surrounding fibroids consist of compressed myometrium containing nerves and blood vessels that continue into adjacent myometrium [33]. Uterine stroma might not allow development of intramural pseudocapsule as in fibroids near endometrial cavity. In addition, one of the most frequently observed endometrial histological changes surrounding submucous LMs is glandular atrophy and ulceration, affecting also the proximal and the distal part of the endometrium over LMs [8]. It is possible that the thickest FP of the submucous LMs will be implicated in the endometrial modification that will consistently reduce the female fertility. FP growth of submucous LMs could reduce and adversely affect the overlying endometrium, becoming atrophic. What is not clear is whether increasing of the FP thickness should increase also the amount of normal quota of neuroendocrine fibers [17]. Normally, both protein gene product 9.5 (PGP9.5) and oxytocin demonstrated no significant differences in the density between the FP and adjacent normal myometrium, regardless of the fibroid location in the uterus. The neuroendocrine PGP9.5 immunoreactive nerve fibers may be involved in the pathophysiology of uterine LMs and affect muscle contractility, uterine peristalsis, and muscular healing.

From the other side, pseudocapsule vasculature present with disarray in vascular architecture with absence of vessel parallelism and variable intervascular distances. The different density of vessels per space indicated an abnormal vascular branching of pseudocapsule and some vascular walls without interruption indicated vessel tortuosity. There were vascular spaces, which did not communicate with other vessels ("cul-de-sac" vessels). All previous data present with geometrical characteristics of malignant neoplasm vessels [18]. From the

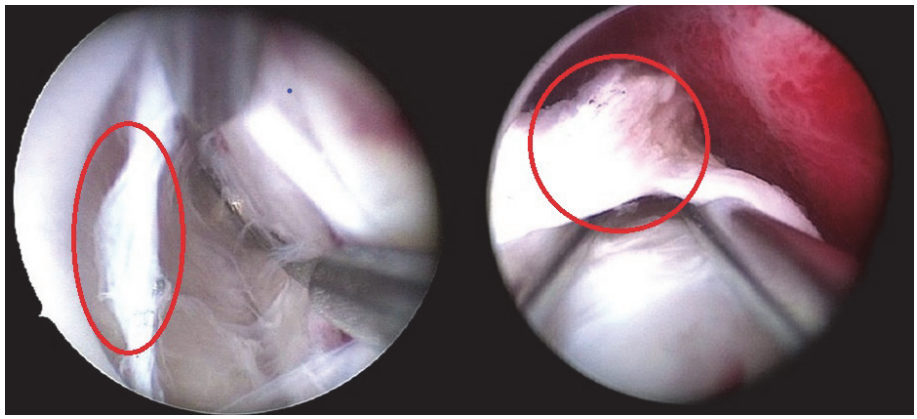

Figure 3: Myoma pseudocapsule in white evidenced by a red circle during a COLD LOOP hysteroscopic myomectomy.

other side, differences in the genetic profile are expressed between fibroids and adjacent endometrium. Angiogenesis promoters' expression is reduced when compared with myometrium while the precursor of angiogenesis inhibitor has reduced expression relative to endometrium. That explains the reduced microvascular density in fibroids relative to endometrium [34]. Obviously, an extended microarray analysis between different location fibroids, its pseudocapsules, and adjacent endometrium need to be performed. Pseudocapsules at different locations need to be examined as different tissues. Given current data, pseudocapsule angiogenesis is increased, even more than nearby myometrium [35]. From these data this is mandated from myometrium but not the fibroid, while MED12 sequence results between pseudocapsule and fibroid, indicate the nontumor origin of the pseudocapsule [24]. In addition, solitary and multiple tumors should be analyzed in different sets, because multiple fibroids originate from MED-12 associated mechanisms while this is not the case for solitary ones [36].

For the importance of FP in myometrium muscle physiology, in case of submucous LMs, the surgical treatment could be not adequate in FP sparing, to save the LMs neurovascular bundle. Considering that the FP should be preserved during myomectomy procedure, the classical hysteroscopic slicing in the context of myometrium could not ensure a "myometrial sparing" approach and therefore the integrity of its pseudocapsule. Recently the "*cold loop*" hysteroscopic myomectomy was reported as a safe and effective procedure for the removal of submucous LMs with intramural development. Such technique allows identifying and sparing the FP (Figure 3) and the surrounding healthy myometrium mechanically, cutting the connective bridges of the FP anchoring the LM to the myometrium, without electricity use [6]. In a retrospective analysis of a large cohort of patients who underwent cold loop myomectomy, Mazzon et al. reported a postsurgical synechiae rate of 4.29%, of which 3.94 were light synechiae removed with the tip of hysteroscope during the follow-up hysteroscopy, 2 months after the surgery. The authors reported that preservation of FP and of myometrial integrity was associated with very few surgical complications and with enhanced healing, reducing risk of uterine rupture, and good fertility rates and delivery outcomes [37].

Concerning intramural LMs, studies have already been published that highlight the importance of intracapsular technique to preserve the myometrium integrity during enucleation of LMs, sparing pseudocapsule (Figure 4) [5, 31]. At the light of the study results and of previous report [38], the authors affirmed that the FP should be always preserved, as much as possible, during the myomectomy procedure, to have a better myometrial cicatrization and a better outcome on successive fertility [17, 31].

6. Conclusions

Considering the increasing interest on the LMs and their fertility implications, the FP evaluation could open new perspectives in clinical research and the treatment of uterine myomas, due to its neuroendocrine and biological role on myometrium and on postsurgical myometrial healing. Our results confirm the relevant difference of FP thickness, particularly thickened under the endometrium for submucous LMs. As the submucous LMs are scientifically largely described as cause of sterility and infertility, FP should be more investigated for possible importance of its preservation in order enhance fertility, also in correlation to postmyomectomy healing and avoiding, i.e., intrauterine adhesion. Future studies should be focused on the correlation between the LMs volume and FP thickness, its amount of neurofibers, and its role on medical, surgery, and fertility outcomes.

Conflicts of Interest

The authors certify that there are no actual or potential conflicts of interest in relation to this article and they reveal any financial interests or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated, including pertinent commercial or other sources of funding for the individual authors or for the associated departments or organizations, personal relationships, or direct academic competition.

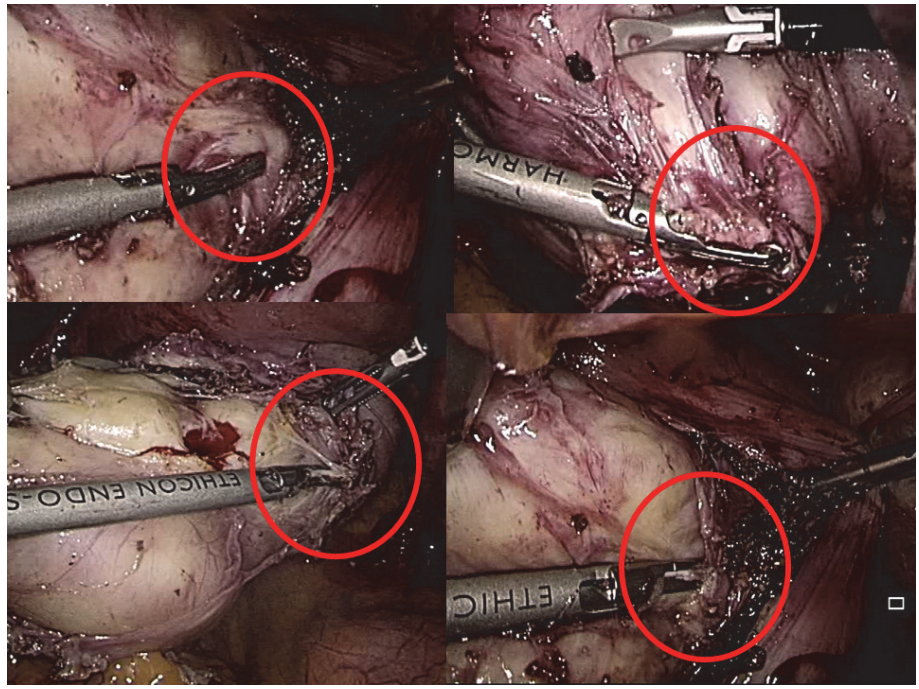

Figure 4: The pseudocapsule of the myoma is highlighted in the red circle: it is incised and cleaved from fibroid with a surgical instrument (to enucleate only the fibroid), preserving the myometrium below the pseudocapsule.

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Research Article

Risk Factors for the Completion of the Cold Loop Hysteroscopic Myomectomy in a One-Step Procedure: A Post Hoc Analysis

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Introduction. The aim of the study was to analyze which variables influenced the completion of a cold loop hysteroscopic myomectomy in a one-step procedure in a large cohort of patients. *Materials and Methods.* A retrospective cohort study of 1434 cold loop resectoscopic myomectomies consecutively performed. The study population was divided into two groups according to the number of procedures needed to accomplish the treatment. Variables influencing the completion of hysteroscopic myomectomy in a one-step procedure were investigated. *Results.* A total of 1434 resections were performed and 1690 myomas in total were removed. The procedure was accomplished in a one-step procedure in 1017 patients (83.7%), whereas 198 women (16.3%) needed a multiple-step procedure. The multivariate analysis showed that the size, the number of myomas, and the age of patients were significantly correlated with the risk of a multiple-step procedure. No correlation was revealed with the grading of myomas, parity, and the use of presurgical GnRH-agonist therapy. *Conclusions.* In case of multiple fibroids, the intramural development of submucous myomas did not influence the completion of cold loop hysteroscopic myomectomy in a one-step procedure. The size of myomas and the age of patients were significantly correlated with the need to complete the myomectomy in a multiple-step procedure.

1. Introduction

Hysteroscopic myomectomy represents the best minimally invasive option for the removal of submucous myomas [1]. Although myomectomy is widely shared and adopted, hysteroscopic treatment of myomas with an intramural extension of 50% or more has always been represented as a challenge for the surgeon, as it influences the possibility of completing the myomectomy in a single-step procedure [1, 2], while increasing the risk for intraoperative complications and repeated surgeries [1, 3, 4]. Moreover, in cases of multiple myomas, the risk is even higher.

As recently reported by Pakrashi, hysteroscopic resection of submucous uterine fibroids should be a simple, well-tolerated, and effective procedure [5]. Several techniques have been reported to date, but the cold loop hysteroscopic myomectomy seems to be the best option, as it allows a safe and complete removal of G1 and G2 myomas in only one-step procedure [1, 6–8]. Different from the classical slicing into the muscular fibers, the cold loop technique allows a safe and complete removal of fibroids characterized by an intramural development, respecting at the same time the surrounding healthy myometrium [1, 6, 8] and the myoma pseudocapsule [9, 10].

The aim of this study was to analyze which patients or myoma characteristics influenced the possibility of completing a cold loop hysteroscopic myomectomy in a single surgical procedure, by assessing a large cohort of patients.

2. Materials and Methods

We retrospectively reviewed from our institutional database the series of consecutive patients who underwent cold loop hysteroscopic myomectomy at the "Arbor Vitae" Centre for Endoscopic Gynecology (Clinica Nuova Villa Claudia, Rome, Italy) between January 2003 and December 2010. Institutional Review Board approval was obtained for data collection.

In order to reduce the potential bias due to the retrospective cohort study design, the patients were selected from our institutional database following the same inclusion and exclusion criteria observed in our previous report in which safety and efficacy of the cold loop were investigated [7]. Clinical data only from patients with a histologic confirmation of a myoma were collected. All the patients were studied by ultrasound and outpatient diagnostic hysteroscopy in order to assess the number, the size, and the grading of myomas, the thickness of the free myometrial margin (FMM), and the thickness of the myometrium between the myoma and the perimetrium. A FMM of at least 2 mm was considered adequate for the treatment because, as demonstrated by Casadio et al., it is not a static parameter but grows progressively with each step of the procedure, leading to an increasing margin of safety [11]. Intramural development was catalogued in accordance with the classification of the European Society of Gynaecological Endoscopy: G0: completely endocavitary, pedunculated myoma, with no intramural extension; G1: submucous myoma with less than 50% intramural extension; G2: submucous myoma with more than 50% intramural extension [2].

In case of fibroids greater than 2 cm, three consecutive injections of gonadotropin-releasing hormone (GnRH) agonist (triptorelin 3.75 mg IM) 28 days apart were administered. A new ultrasound scan was carried out after the GnRH-agonist therapy and a 15% reduction in size of submucous myomas was registered.

Before the surgery, informed consent was obtained from all the patients. G1 and G2 fibroids were treated by using the cold loop hysteroscopic myomectomy as previously described [6, 7]. As the cold loop technique was conceived for the treatment of myoma with an intramural component, G0 myomas were enrolled only if present at the same time with G1-G2 fibroids and removed by means of the traditional slicing technique. All the procedures were performed by 4 surgeons with the same experience and skill level, using a 9 mm resectoscope with 0° optical system (HOPKINSII® Karl Storz, Tuttlingen, Germany) and 1.5% glycine for distention of the uterine cavity. Slicing was performed using an electric loop powered by a 100 W monopolar current in pure cutting mode, whereas the enucleation of the intramural component was performed with a nonelectric mechanical loop (Mazzon's cold loops®, Karl Storz, Tuttlingen, Germany). In order to reduce thermal damage of the healthy myometrium as much as possible, coagulation was never used. The continuous and constant irrigation of the distention media was provided by HYDROMAT® (Karl Storz, Tuttlingen, Germany). The intrauterine cavity pressure was set between 90 and 110 mmHg depending on the type of intervention. The liquid balance was monitored by EQUIMAT® (Karl Storz, Tuttlingen, Germany). When the level of absorbed liquid reached 1000 cc or the serum sodium dropped to 125 mEq/l, the myomectomy procedure was interrupted and a second surgery was scheduled. Antibiotic prophylaxis was only administered to patients with specific indications (e.g., cardiac valvulopathies).

Clinical data was collected regarding the characteristics of patients and their obstetric history. Number, size, and grading of myomas as well as the length of surgery (from the introduction of the resectoscope in the uterine cavity until the end of the procedure) were analyzed.

In order to investigate the variables that influenced the need for a multiple-step procedure to completely remove the myomas from the uterine cavity, the study population was divided into two groups: patients who completed the treatment in a single procedure (one-step group, OS) and the patients who accomplished the myomectomy in two or more procedures (multiple-step group, MS). A multivariate analysis was then carried out in order to eliminate confounding factors. In the event of multiple myomas, the grading and size were considered as the mean of the enucleated fibroids.

2.1. Statistical Analysis. The Mann–Whitney test was used to compare ordinal and non-normally distributed continuous variables (deviation from Gaussian distribution was checked by using the Shapiro-Wilk test). Categorical data were analyzed by a $\chi 2$ test with Yate's correction. A multivariate logistic regression model was fit to the prediction of a cold loop hysteroscopic myomectomy in a single-step surgical procedure (coded as yes = 1 and no = 0), incorporating as explanatory variables all the variables that showed a p value ≤ 0.25 in bivariate analysis [12]. The goodness of fit for logistic regression models was checked using the Hosmer and Lemeshow test. Statistical analyses were performed using IBMSPSS ® version 22.0 (IBM Corp., Armonk, NY, USA, 2013). A two-sided p value < 0.05 was considered significant.

3. Results

A total of 1215 patients were selected during the study period. There were 1434 resections performed and 1690 myomas in total were removed. The indications for resectoscopic myomectomy were heavy menstrual bleeding in 51.43% and 21.12% of cases in the OS and MS groups, respectively, with infertility (OS 9.3% and MS 3.12%) and intermenstrual spotting (OS 9.82% and MS 0.37%). In 4.84% of cases, the indication was postmenopausal bleeding and in 2.05% of cases there was a thickening of the endometrium, subsequently diagnosed as a myoma.

The cold loop hysteroscopic myomectomy was accomplished in a one-step procedure in 1017 patients (83.7%), whereas 198 women (16.3%) needed a multiple-step procedure. No major complications occurred. Twelve minor intraoperative complications were recorded (0.84%). The characteristics of the patients and myomas are summarized in Table 1.

The mean age was significantly higher in the OS group ($p = 0.0001$), whereas the number of patients who were given the GnRH agonist was significantly higher in the MS group ($p = 0.0001$). The size of G1 and G2 myomas was significantly higher in the MS group than in the OS group (0.0001). Multiple fibroids were significantly more numerous in the MS group ($p = 0.028$). The length of procedures was significantly higher in the MS group than in the OS group ($p = 0.0001$).

The characteristics of treated myomas in each group are shown in Table 2 according to size and intramural development. The number of removed G1 and G2 myomas

Table 1: Characteristics of patients.

	One-step group (OS)	Multiple-step group (MS)	Total	p
Patients	1017 (83.7)	198 (16.3)	1215	-
Procedures	1017 (70.92)	417 (29.08)	1434	-
Age (years)*	43.13 ± 8.24	40.42 ± 6.08	42.69 ± 7.99	0.0001
Nulliparous	640 (62.9)	135 (68.2)	775	0.216
Pluriparous	377 (37.1)	63 (31.8)	440	
Previous cesarean section	159 (15.6)	26 (13.1)	185 (15.2)	0.415
GnRH agonist	445 (43.8)	134 (67.7)	579 (47.6)	0.0001
Length of procedures (minutes)*	14.16 ± 9.24	19.08 ± 14.16	16 ± 11.05	0.0001
G0	34 (2.89)	13 (2.54)	47 (2.78)	0.75
G1	753 (63.92)	285 (55.66)	1038 (61.42)	0.0016
G2	391 (33.19)	214 (41.8)	605 (35.8)	0.0008
G0 size (mm)*	18.03 ± 7.82	18.31 ± 8.45	18.11 ± 7.9	0.865
G1 size (mm)*	20.94 ± 8.79	24.12 ± 11.21	21.81 ± 9.62	0.0001
G2 size (mm)*	22.49 ± 9.11	28.6 ± 10.5	24.66 ± 10.05	0.0001
Single myoma procedures	901(88.6)	351 (84.2)	1252 (87.3)	0.028
Multiple myomas procedures	116 (11.4)	66 (15.8)	182 (12.7)	
Total myomas removed	1178 (69.7)	512 (30.3)	1690	0.023

Data as reported as n (%) p = $\chi 2$ test with Yate's correction
∗ mean ± SD p = Mann–Whitney test.

Table 2: Number of myomas treated according to the size (mm).

	G0			G1			G2		
One-step procedures	>40	40-20	<20	>40	40-20	<20	>40	40-20	<20
	0 (0)	18 (52.9)	16 (47.1)	12 (1.6)	471 (62.5)	270 (35.9)	13 (3.3)	260 (66.5)	118 (30.2)
Multiple-step procedures	>40	40-20	<20	>40	40-20	<20	>40	40-20	<20
	0 (0)	7 (53.8)	6 (46.2)	20 (7)	172 (60.4)	93 (32.6)	30 (14)	149 (69.6)	35 (16.4)
p	0	0.955	0.955	0.0001	0.562	0.368	0.0001	0.486	0.0003

Data are reported as n (%)
p = $\chi 2$ test with Yate's correction.

greater than 40 mm was significantly higher in the MS group than in the OS group (p = 0.0001). No statistically significant differences were found between the two study groups in the number of G2 and G1 myomas measuring from 20 to 40 mm.

Finally, a multivariate analysis was carried out in order to assess which variables significantly influenced the completion of the hysteroscopic myomectomy in one surgical procedure (Figure 1). The size and the number of myomas and the age of patients were significantly correlated with the need to complete the myomectomy in a multiple-step procedure. No correlation was revealed with the grading of myomas, nor with parity or the use of presurgical GnRH-agonist therapy.

4. Discussion

The grading of myomas has always been considered a major difficulty in hysteroscopic myomectomy, especially when associated with multiple myomas [3]. In 1993, Wamsteker [2] recommended treating myomas with more than 50% intramural extension only in selected cases, as repeated procedures were usually needed in order to achieve complete resection and resolution of symptoms. Recently, multiple variables and not only the degree of myometrial penetration were considered in the "STEPW classification" proposed by Lasmar et al. [13], to more accurately predict a complete or an incomplete removal of the myoma before treatment. The size of myoma, its topography, the extension of its base, and its penetration into the myometrium all seem to influence the outcome of surgery in a hysteroscopic myomectomy [14]. Nevertheless, we believe that these factors should be correlated with the technique utilized and the number of myomas present in the uterine cavity at the same time.

The matter of treating the intramural extension of myomas in order to resolve the related clinical symptoms has been stressed over the last three decades and with this purpose several techniques have been described [1]. Some have been conceived as a "two-step procedure" [15, 16], but they are burdened with a double anesthetic and surgical risk for the patients; other techniques were instead conceived as a "one-step procedure", with the aim of accomplishing the myomectomy in only one surgical session [17–21]. In the latter case, the skill level of the surgeon and the characteristics of the myoma may determine the success of the hysteroscopic myomectomy. But when we deal with cold loop hysteroscopic

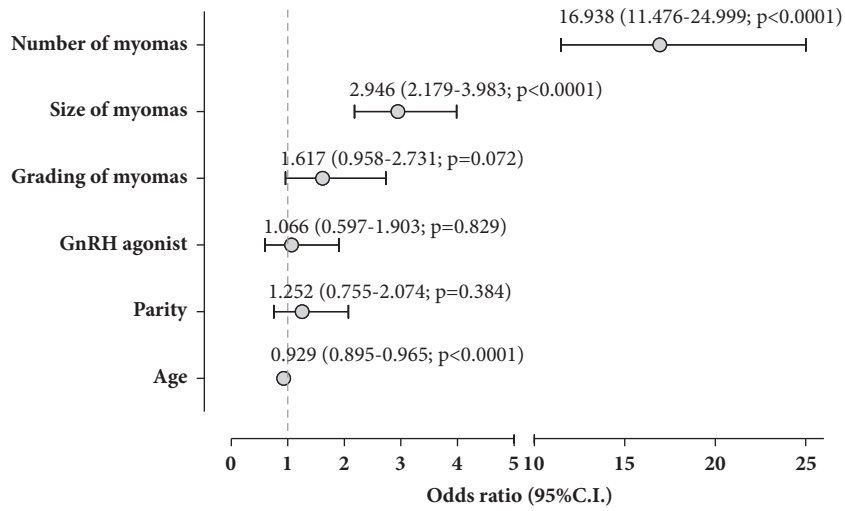

Figure 1: Multiple logistic regression model of variables influencing the multiple-step procedure. In order to scale OR in a more intelligible range, size of myomas is expressed as mean (cm) of all myomas treated in each patient. Grading of myomas is expressed as mean of all myomas treated in each patient. Multivariate logistic regression model was fit to the prediction of a cold loop hysteroscopic myomectomy in a single-step surgical procedure (coded as yes = 1 and no = 0), incorporating as explanatory variables all the variables that showed a p value ≤ 0.25 in bivariate analysis [11]. The goodness of fit for logistic regression models was checked using the Hosmer and Lemeshow test.

myomectomy, which is a highly recognized procedure useful to remove single or multiple myomas respecting the pseudocapsule [22–25], we may consider that myoma progressively moves during surgery from the inner myometrium to the endocavitary region.

The cold loop technique allows treating the intramural component of G1 and G2 myomas by the blunt dissection of the fibroconnectival bridges which anchor the myoma to the pseudocapsule [22, 26]. In this way, the intramural portion of the myoma slides in the uterine cavity becoming an intracavitary lesion, easy to treat by classical slicing. Therefore, the intramural component of myoma loses its importance and the most difficult phase of the procedure is dependent on the size rather than on the myoma grading.

Although a correct comparison is difficult and risks are being somewhat arbitrary, our results seem to be in agreement with the available literature [1–3, 14, 27–29] as well as with the results previously reported by Leone using the cold loop technique [30]. Indeed, in our series 1017 patients (83.7%) accomplished the treatment in a one-step procedure. Therefore, differently from the intramural slicing, which inevitably damages the surrounding healthy myometrium because of the fibers cutting and the thermal damage, the cold loop myomectomy enables an effective treatment of G1 and G2 myomas, with a low rate of intraoperative complications and virtually eliminating uterine perforation with thermal loops [6, 7].

In a previous study, we evaluated the chance of completing the treatment in a single step with the cold loop hysteroscopic myomectomy and, in order to avoid confounding factors, we selected a cohort of patients with only a single myoma. The results showed that the size, the grading of myomas, and the age of patients were the independent variables that influenced the completion of procedures in only one surgical step [8]. Different from the aforementioned investigation, in the present study, we selected all the patients from our institutional database, including those treated with multiple myomas and the grading of myomas seems to lose its important role. Indeed, the logistic regression analysis showed a minor importance of the intramural development and a significant role of number and size of myomas and the age of patients (P = 0.0001). We speculate that these contradictory results may be justified by the inclusion of patients with multiple myomas. The analysis of surgical procedures in two different populations of patients cannot be considered in the same way. In the first study [8], we provided the information to the surgeon that, if a single myoma has to be removed with this technique, a special care should be given to the size and the grading of the fibroid. This study, on the contrary, provides different recommendations in case of patients with multiple myomas. As predictable, the surgeon should be aware that size and number are related to a multiple-step procedure, but not the intramural component of fibroids.

Concerning the myomas size, it should be underlined that, with increasing diameter, the volume of myoma increases much faster (to the third power). As reported by Emanuel, this is of great influence on the ultimate surgery time that is necessary for the complete removal of myoma by hysteroscopic techniques [31]. In our series, the G2 myomas in MS group were double in volume with respect to the G2 in OS group. Indeed, a multivariate analysis demonstrated that the risk of a multiple-step procedure increased by about 3 times for each centimeter of myoma (O.R. 2.946; p < 0.0001).

In our experience, the age of patients was inversely correlated with a multiple-step procedure. We speculate that a possible explanation for this phenomenon is myometrial dysfunction, which is detectable in women over the age of 40 [32–34]. Indeed, both blood supply and the absorption of distention media are decreased because of reduced uterine

vascularization, which is characteristic of women approaching menopause.

The GnRHa administration before surgery was not correlated with multiple-step procedure. We speculate that this issue could be a bias due to the retrospective analysis of data. Indeed, the lack of estrogens induced by GnRHa administration, as clearly demonstrated by De Falco et al., affects both the fibroid and the uterus compacting the tissue including the pseudocapsule, increasing the difficulty of the myoma dissection from the surrounding myometrium [35]. Recently, we published a RCT with the aim of evaluating the intraoperative effects of GnRHa pretreatment in patients undergoing cold loop hysteroscopic myomectomy. The results showed that the preoperative GnRHa administration did not facilitate the completion of cold loop hysteroscopic myomectomy in a single surgical procedure in G2 myomas and was correlated with a longer duration of the surgery. No significant benefits were found for G0 and G1 myomas [36].

The four expert surgeons, with a high experience in cold loop myomectomy, could represent the main limitation of this retrospective study. Indeed, the cold loop technique requires an adequate surgical experience [1], yet we believe that, as already demonstrated [6, 7, 30, 37], with an acceptable learning curve it is possible to safely carry out a satisfying procedure with excellent outcomes.

5. Conclusions

In conclusion, we can affirm that, in case of multiple G1 and G2 myomas, the intramural development did not influence the completion of the cold loop hysteroscopic myomectomy in a single procedure. Nevertheless, the size of myomas and the age of patients were significantly correlated with the need to complete the myomectomy in a multiple-step procedure. In the presence of these risk factors, the option of a second-step procedure should be taken into consideration by the surgeon.

The low rate of complications, the number of treatments accomplished in a single procedure, even in case of multiple myomas, and the fact that myomectomies were performed by 4 different surgeons point out that cold loop technique is not only safe and effective, but also repeatable.

Conflicts of Interest

Ivan Mazzon reports nonfinancial support from Storz, Tuttlingen, Germany, outside the submitted work. Alessandro Favilli, Mario Grasso, Stefano Horvath, Vittorio Bini, Gian Carlo Di Renzo, and Sandro Gerli report no conflicts of interest.

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Research Article

Does Uterine Fibroid Adversely Affect Obstetric Outcome of Pregnancy?

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Background. Fibroid is the most common benign tumor of the uterus and if associated with pregnancy may adversely affect the outcome of pregnancy. Objective of the present study was to assess the obstetric outcome (maternal and fetal) in pregnancy with fibroid. *Methods.* A prospective observational study was performed over a period from May 2015 to August 2017 at Obstetrics and Gynecology Department in Zagazig University Hospitals, Egypt. 64 pregnant patients with >2 cm fibroid were taken in the study. Routine fundamental investigations were done for all. They were followed during antenatal period clinically and scanned by ultrasonogram which was done at booking visit and during subsequent visits to assess the change in the size of the fibroid and other obstetric complications. Maternal age, parity, size of fibroid, complications during pregnancy, and mode of delivery were noted. *Results.* 64 pregnant patients with uterine fibroids were recruited; 47 of them completed the study to the end. The average age was 31.80 ± 3.27 years, body mass index (BMI) [calculated as weight in kilograms divided by the square of height in meters] was 24.67 ± 2.46, primigravida was 23.4%, multigravida was 76.6%, duration of menstrual cycle/day was 29.68 ± 3.10, and duration of menstrual period/day was 6.46 ± 1.12. The percentage of spontaneous conception was 59.57% and 40.43% for using assisted reproductive technology. The results of obstetric outcome were spontaneous abortion in 2%, premature delivery in 27.7%, and delivery at 37–41 weeks of pregnancy in 70.2%. The mode of delivery was vaginal delivery in 15% and cesarean sections in 85%. Also, 34% had threatened miscarriage, 21% had preterm labor, 2% had antepartum bleeding in the form of placenta previa, 4% had abdominal pain needing admission, one of them underwent laparotomy and was diagnosed as red degeneration, 2 (4%) had postpartum hemorrhage, and only one needed blood transfusion. Cesarean sections were done in 85%. Neonatal outcome was acceptable with no perinatal mortality. There were no significant differences between patients with single or multiple fibroids as regards the obstetric outcome or type of fibroid either intramural or subserosal. The obstetric outcomes were not significantly affected by the number, size, or type of fibroids. *Conclusions.* Even most of fibroids in pregnancy are asymptomatic but may be associated with some complications affecting the course of pregnancy and labor. So, pregnancy has to be cautiously screened in the antenatal period, through regular follow-up, to detect any adverse obstetric complications and so improve the outcome.

1. Introduction

Myomas are the most frequently recorded benign smooth muscle tumor of the uterus, affecting 20%–60% of women of reproductive age and may negatively affect fertility and outcome of pregnancy [1]. As most fibroids are asymptomatic, the true prevalence of fibroids may be greatly higher [2]. The incidence of fibroids in pregnancy reported ranges from 0.1 to 10.7% of all pregnancies and increases as the female chooses to postpone pregnancy later on [3]. It was found that 10%–40% of prepartum complications which happened in pregnancy with fibroid have been associated with the presence of it [4].

Myomas have been complicated by changes like degeneration leading to abdominal pain whose severity is varied from mild to acute abdomen [5]. Also, they are related to a lot of ante-, intra-, and postpartum complications like spontaneous abortion, antepartum hemorrhage, placental abruption, malposition of the fetus, fetopelvic disproportion, premature rupture of membranes, retention of the placenta,

postpartum hemorrhage (PPH), preterm delivery, low birth weight infants, dysfunctional labor, and increased need to cesarean deliveries [6].

The principal aim of this study was to inspect obstetric outcomes (maternal and fetal) of pregnancies with fibroids and any associated complications. Furthermore, the secondary aim was about the modification of antenatal care of such patients to improve the outcomes.

2. Patients and Methods

64 patients signed up in this current prospective observational study. Their age ranged from 22 to 43 years. They were recruited from antenatal clinics at Obstetrics Department in Zagazig University Hospitals with pregnancy with fibroid after attending first-trimester ultrasonography examination which diagnosed them. They underwent both consequent antenatal care and delivery at the study institute in the study time. Ultrasonogram was done at successive visits to evaluate the change in the size of the fibroid and any associated complications either in fibroid or in pregnancy in general. The period of study was from May 2015 to August 2017. Patients with fibroid of ≥2 cm were included in the study. Excluded criteria were history of any surgical manipulation of uterus such as cesarean section, resection of uterine septum or myomectomy, any uterine malformation, adenomyosis (uterine adenomyoma), any general disease, for example, cerebrovascular, cardiovascular, or diabetes mellitus, and renal insufficiency. After the protocol of this study was approved by the research ethics committee of Zagazig University Hospitals, informed consent (verbal and written) was obtained from all participants. Full patient history, clinical examination, and demographic data were recorded. All participants undertook booking ultrasonographic examination then repeated in every antenatal care with detailed obstetric report with comment on any adverse episodes related to characters of fibroid as size, number, place, and so forth). Measurements at 12–16 weeks were used as reference and compared with those which were taken at 22–26 weeks and 28–34 weeks of pregnancy. The information of obstetric occasions throughout antenatal period and delivery were recorded. Observations of patients till the end of puerperal period were also documented. Qualitative variables were expressed as frequency and percentage, compared using the Pearson χ^2 test, continuity correction χ^2 test, and the Fisher exact test. Quantitative variables were expressed as mean ± SD and compared using the Student t-test, Mann–Whitney U test, analysis of variance, and the paired Student t-test. All data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

3. Results

Present study included 64 women who were having pregnancy with uterine fibroids. Fibroids that are more than or equal to 2 cm were included in the study.

10 patients were excluded due to deviation from the inclusion criteria; three had previous cesarean sections, one had previous myomectomy, one had uterine malformation, one had uterine adenomyosis, and 4 had medical disorder (two had history of diabetes mellitus and one had history of chronic hypertension).

Table 1: Demographic characteristics.

Variable	Number of OR (mean ± SD)	Percentage %
Age	31.80 ± 3.27	
Prepregnancy body mass index (BMI)	24.67 ± 2.46	
Gravidity		
Primigravida	11	23.4
Multigravida	36	76.6
Duration of menstrual cycle/day	29.68 ± 3.10	
Duration of menstrual period/day	6.46 ± 1.12	
Spontaneous conception	59.57%	28
Using assisted reproductive technology	40.43%	19

Values are given as mean ± SD or number (percentage %).

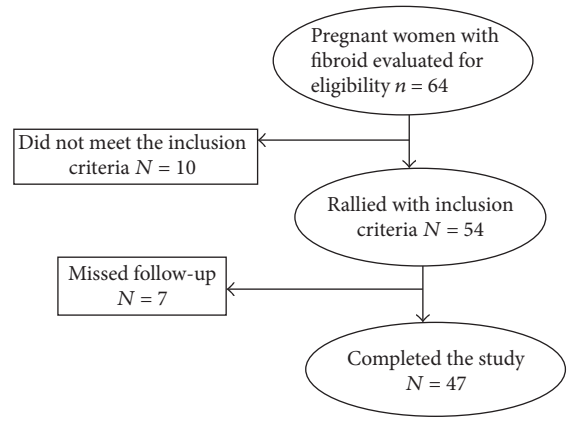

Figure 1: Participants of the study in flow chart.

The follow-up of 7 cases was lost. So, ending data were included from 47 patients only (Figure 1). Ultrasonic examinations of the fibroid at 10–14 weeks, 20–24-weeks, and 28–34 weeks were recorded and studied statistically.

The average of demographic data were as follows: for *age* 31.80 ± 3.27 years, *body mass index* (BMI) [calculated as weight in kilograms divided by the square of height in meters] 24.67 ± 2.46, *gravidity* 2.63 ± 1.21, parity 1.26 ± 1.03, *duration of menstrual cycle/day* 29.68 ± 3.10, and *duration of menstrual period/day* 6.46 ± 1.12.

The percentage of spontaneous conception was 59.57% and 40.43% for using assisted reproductive technology (Table 1).

Maternal outcome during antenatal period was represented in Table 2. 16 (34%) had threatened miscarriage (vaginal bleeding occurring at <28 weeks of pregnancy), 10

Table 2: Maternal outcome during antenatal period.

Outcome	Number (N)	Percentage (%)
Threatened miscarriage	16	(34%)
Preterm labor	10	(21%)
Antepartum bleeding—placenta previa	1	(2%)
Abdominal pain needing admission	2	(4%)
Laparotomy due to pain	1	(2%)
Postpartum hemorrhage	2	(4%)
Blood transfusion	1	(2%)

Values are given as number (percentage %).

Table 3: Pregnancy outcome.

Outcome	Number (N)	Percentage (%)
Spontaneous abortion	1	(2%)
Premature delivery	13	(27.7%)
Delivery at 37–41 weeks	33	(70.2%)
Vaginal delivery	7	(15%)
Cesarean sections	39	(85%)

Values are given as number (percentage %).

Table 4: Neonatal outcome.

Outcome	Number (N)	Percentage (%)
Congenital anomaly	1	2%
Fetal weight	2978.15 ± 374	
Apgar score		
(i) Apgar score ≤ 7 at 1 minute	2	4%
(ii) Apgar score ≤ 7 at 5 minutes	1	2%
(iii) Apgar score at ≤ 7 at 10 minutes	0	0
Neonatal admission (NICU)	0	0

Values are given as mean ± SD or number (percentage %).

(21%) had preterm labor, 1 (2%) had antepartum bleeding in the form of placenta previa, 2 (4%) had abdominal pain needing admission, one of them underwent laparotomy and was diagnosed as for red degeneration, 2 (4%) had postpartum hemorrhage (estimated blood loss ≥ 1000 mL for cesarean deliveries or ≥500 mL for vaginal deliveries), and only one needed blood transfusion. Table 3 showed pregnancy outcome (spontaneous abortion 1 (2%), premature delivery (delivery at 28–<37 weeks of pregnancy) 13 (27.7%), or delivery at 37–41 weeks of pregnancy 33 (70.2%)) and also the mode of delivery {vaginal delivery in 15% or cesarean sections in 85%}. Neonatal outcome represented in Table 4 showed that only one neonate had congenital anomaly in the form of cleft palate. The average fetal weight was 2978.15±374 with good Apgar score with no perinatal mortality. There were no significant differences between patients with single or multiple fibroids as regards the obstetric outcome (Table 5) or type of fibroid either intramural or subserosal (Table 6). The changes in size of fibroid through the pregnancy were represented (Table 7). There was a significant increase in fibroid size only between the 14–16-week and 22–26-week examinations and also between 11–14-week and the 28–34-week examinations when fibroids were below 2 cm in diameter.

4. Discussion

The size, number, and type of fibroids had no significant importance with occurrence of adverse outcomes in this current study. This agreed with the study of Klatsky et al. 2008 [7] and study of Poovathi and Ramalingam 2016 [8]. Even Stout et al. 2013 discussed the adverse effect of fibroid on twins pregnancy and also found no significant relations [9]. On general the fibroids did not have significant adverse effects on obstetric outcomes either maternal or neonatal in current study.

Follow-up of the size of fibroid during antenatal period showed a significant increase in size between 14–16 weeks and 22–26 weeks and between 14–16 weeks and 28–34 weeks in fibroids that were ≤3 cm in diameter at the earliest scan and these results were of the same opinion of Wang et al. 2016 [10]. As regards the fibroid type (intramural and subserosal), it was not associated with adverse obstetric outcomes. Size of fibroid has been associated with increased admissions for fibroid pain, postpartum hemorrhage, postpartum blood transfusions, or increased blood loss in some studies like those of Lam et al. 2014 [11] and Shavell et al. 2012 [12] but in our study we did not find that.

There was no significant difference in the occurrence of adverse effects in pregnancy with single or multiple fibroids in the present study although the power of the number of fibroids on obstetric outcomes in some studies is still divisive. Lam et al. [11] reported a higher rate of preterm delivery among patients with multiple fibroids compared with those with a single fibroid. Likewise, Ciavattini et al. [13] monitored raised preterm delivery, cesarean delivery, and breech presentation rates among individuals with multiple fibroids compared with single fibroids or no fibroids.

However, Qidwai et al. [14] reported no correlation between increased numbers of fibroids and adverse obstetric outcomes and Lai et al. [15] recorded no relationship between preterm delivery and fibroid number.

In our study, vaginal delivery was less than cesarean section. In various studies, rate of cesarean section ranges between 34% and 73%. Klatsky et al. 2008 recorded that women with fibroids were at a 3.7-fold increased risk of cesarean delivery [7]. Vergani et al. 2007 reported that multiple fibroids, large fibroids, and fibroids in the lower uterine segment are predisposing factors for cesarean delivery [16]. Changes in fibroids during pregnancy stay divisive. In the current study, fibroids ≤ 2 cm at first evaluation increased in size whereas fibroids that were ≥2 cm showed no change in size during the second trimester. Benaglia et al. reported significant fibroid growth during early pregnancy and explained human chorionic gonadotropin as an important contributing factor [17]. Lev-Toaff et al. described that fibroids either increased in size or remained unchanged, in response to increased estrogen in the first trimester, and in

Table 5: Obstetric outcomes between patients with single or multiple fibroids.

Outcomes	Patients with single fibroid (N)	Patients with multiple fibroids (N)	P value
Threatened miscarriage (16)	9	7	0.077
Preterm labor (10)	4	6	0.88
Antepartum bleeding—placenta previa (1)	1	0	0.96
Abdominal pain needing admission (1)	1	0	0.96
Laparotomy due to pain (1)	0	1	0.96
Postpartum hemorrhage (2)	1	1	1.0
Blood transfusion (1)	1	0	0.96
Spontaneous abortion (1)	0	1	0.96
Premature delivery (13)	8	5	0.187
Delivery at 37–41 weeks (33)	19	14	0.586
Vaginal delivery (7)	3	4	0.97
Cesarean sections (39)	22	17	0.123

Values are given as number; $P < 0.05$ was considered statistically significant.

Table 6: Obstetric outcomes between patients with different types of fibroid.

Outcomes	Patients with intramural fibroid (N)	Patients with subserosal fibroid (N)	P value
Threatened miscarriage (16)	6	10	0.97
Preterm labor (10)	3	7	0.78
Antepartum bleeding—placenta previa (1)	0	1	0.97
Abdominal pain needing admission (1)	1	0	0.96
Laparotomy due to pain (1)	1	0	0.98
Postpartum hemorrhage (2)	2	0	0.841
Blood transfusion (1)	1	0	0.96
Spontaneous abortion (1)	0	1	0.96
Premature delivery (13)	6	7	0.98
Delivery at 37–41 weeks (33)	17	16	0.76
Vaginal delivery (7)	5	2	0.68
Cesarean sections (39)	27	12	0.83

Values are given as number; $P < 0.05$ was considered statistically significant.

Table 7: Alteration in size of fibroid during pregnancy.

Time of assessment	Fibroids ≤ 3 cm in diameter at participation	Fibroids ≥ 3 cm in diameter at participation
Assessment at 14–16 weeks of pregnancy	1.96 ± 0.82	3.98 ± 1.16
Assessment at 22–26 weeks of pregnancy	2.48 ± 1.27	4.93 ± 1.05
Assessment at 26–34 weeks of pregnancy	3.54 ± 0.96	5.14 ± 1.23
P value		
(i) Comparing 1, 2	0.04	0.74
(ii) Comparing 2, 3	0.81	0.23
(iii) Comparing 1, 2	0.02	0.19

Values are given as mean ± SD; $P < 0.05$ was considered statistically significant.

the second trimester, smaller fibroids (2–6 cm) increased in size or remained unchanged while larger fibroids (>6 cm) decreased in size, maybe due to the starting of estrogen receptor downregulation. Lastly, during the third trimester, fibroids decreased in size or stayed unchanged because of estrogen receptor downregulation [18]. On the other hand, Rosati et al. reported that 69% of pregnant women who had a fibroid practiced no increase in fibroid volume [19]. Laughlin et al. proofed reduction in fibroid size during pregnancy [20]. Consistently, our results somewhat agreed with the findings of Lev-Toaff et al. Nevertheless, it is impractical to expect the growth of fibroids perfectly as fibroids responding to pregnancy in a dissimilar way in different individuals [18]. Moreover, no studies have yet illuminated the effects of several confusing factors on the growth of fibroids in pregnancy.

5. Strengths and Limitations of the Study

Our study had *limitations* of being just observational one not having a comparing group, the sample size was small, some popular concepts could have resulted in a high cesarean delivery rate, and all patients included in the study had no submucosal fibroids. The agreement of our results with the previous studies strengthened the current study.

6. Conclusion

Pregnant patients who have fibroids were exposed to high incidence of complications throughout antepartum, intrapartum, and postpartum period. So, they have to be carefully screened in the antenatal period through regular follow-up. Most of the fibroids are asymptomatic but may adversely affect the path of pregnancy and labor dependent on their location and size. The broad employment of ultrasonography has simplified diagnosis and management of fibroids in pregnancy.

Ethical Approval

The study was approved by the institutional ethics committee.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

The Investigation and Management of Adenomyosis in Women Who Wish to Improve or Preserve Fertility

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The management of adenomyosis remains a great challenge to practicing gynaecologists. Until recently, hysterectomy has been the only definitive treatment in women who have completed child bearing. A number of nonsurgical and minimally invasive, fertility-sparing surgical treatment options have recently been developed. This review focuses on three aspects of management, namely, (1) newly introduced nonsurgical treatments; (2) management strategies of reproductive failures associated with adenomyosis; and (3) surgical approaches to the management of cystic adenomyoma.

1. Introduction

Adenomyosis is a common benign gynaecological condition but its diagnosis and treatment remain a clinical challenge to physicians. The true incidence of adenomyosis is unknown and the prevalence varies widely due to the lack of a standardized definition and diagnostic criteria. The prevalence from previous retrospective cohort and prospective cohort observational studies is summarized in Tables 1 and 2 [1–9]. Adenomyosis also commonly occurs together with endometriosis. Di Donato et al. [10] showed a prevalence of 21.8% in women undergoing surgery for endometriosis. They also showed an association with parous women, increasing age, dysmenorrhea intensity, and presence of deep infiltrating endometriosis.

Adenomyosis is best defined by Bird in 1972 as "the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium" [11].

2. Pathogenesis

The exact pathogenesis of adenomyosis remains debatable. The diagnosis of adenomyosis is made when ectopic endometrial implants are found within the myometrium of the uterus. The most common and widely accepted theory involves the downward invagination of the endometrial basalis layer into the myometrium due to either myometrial weakness or altered immunologic activity leading to disruption of the endometrial-myometrial interface, also known as the "junctional zone (JZ)" [12]. Leyendecker et al. [13] showed that uterine auto-traumatisation and the initiation of the mechanism of tissue injury and repair (TIAR) as the primary cause for adenomyosis development based on their method of "visualization" by transvaginal ultrasound (TVS) and cinematographic magnetic resonance imaging (MRI). Their group showed the archimetral compression from the neometral contraction at the onset of menstruation causes high intrauterine pressure, leading to rupture of the archimyometrium at cornual angles. Thus, fragments of the basal endometrium are then detached and deposited into the myometrial wall where they develop into endometriotic cysts. In addition, as the basal stromal cells at the fundo-cornual raphe are chronically over stretched, it initiates the TIAR mechanism and development of an adenomyoma. Other theories include de novo development from embryonic-misplaced pluripotent Mullerian remnants or invagination along the intramyometrial lymphatic system or displaced bone marrow stem cells [14].

Table 1: Prevalence of adenomyosis after hysterectomy specimens for various gynaecological conditions (from retrospective cohort studies).

Study	Vercellini et al. 1995 [1]	Vavilis et al. 1997 [2]	Seidman and Kjerulff1996 [3]	Parazzini et al. 1997 [4]	Bergholt et al. 2001 [5]
Number of cases (*n*)	1334	594	1252	707	549
Adenomyosis (%)	25	20	12–58	21	10–18
Uterine fibroid	23	21		15	
Genital prolapse	26	26		30	
Ovarian cyst	21	18		30	
Cervical cancer	19	18		25	
Endometrial cancer	28	16			
Ovarian cancer	28	21			

3. Diagnosis

Histological examination is the gold standard in the diagnosis of adenomyosis, even though the exact histological criteria have not been universally agreed. One accepted criterion is the presence of endometrial tissue more than 2.5 mm below the endomyometrial junction or a JZ thickness of more than 12 mm [15]. The modification of the uterine structure may range from thickening of the JZ of >12 mm to nodular or diffuse lesions involving the entire uterus. Thus, adenomyosis is classified to "diffuse adenomyosis" where endometrial deposits are found dispersed within the myometrium or "focal adenomyoma" where the endometrial deposits are more localized at one site within the uterine wall as a confined lesion [14].

Apart from the findings of these ectopic endometrial tissues within the myometrium, smooth muscle changes like hyperplasia are often found. Ultrastructural differences between smooth muscle cells from adenomyosis and normal uterus were found with myocytes showing cellular hypertrophy, differences in cytoplasmic organelles, nuclear structures, and intercellular junctions [15]. The myocytes in adenomyosis also lack the cyclical changes present in myocytes of the normal uterus [16].

4. Cystic Adenomyoma

Rarely, adenomyosis may present as a cystic lesion lined with endometrial tissue and surrounded by myometrial tissue when it is called "cystic adenomyoma." Juvenile cystic adenomyoma (JCA) is a subgroup of cystic adenomyoma that commonly occurs in adolescents or women < 30 years of age and is not associated with diffuse adenomyosis. Takeuchi et al. [17] proposed the following diagnostic features of juvenile cystic adenomyoma (JCA): (1) age < 30 years; (2) cystic lesion of >1 cm in diameter independent of the uterine lumen and covered by hypertrophic myometrium on diagnostic images; and (3) association with severe dysmenorrhea. They found that laparoscopic excision of the lesion demonstrated significant improvement of dysmenorrhea in these cases.

5. Presentations

The classic presentation of adenomyosis is heavy, painful menstrual bleeding, typically occurring in multiparous women between 40 and 50 years of age [14]. Heavy menstrual bleeding is present in up to 40–60% of patients, which may be due to the enlarged endometrial surface area or the increased vascularity of the endometrium [14]. Dysmenorrhea occurs in 15–30% of patients, which may be related to the swelling of endometrial tissue within the myometrium or increased production of prostaglandin within the myometrium [18]. Both the amount of bleeding and degree of pain were shown to be significantly correlated with the degree of myometrial invasion [18]. Other presenting features include chronic pelvic pain, dyspareunia, and the finding of an enlarged uterus in an asymptomatic subject. Women with adenomyosis had been shown to have a decreased quality of life [19], up to 33% of patients may be asymptomatic, and the diagnosis of up to 30% of patients was only made by histology following a hysterectomy [20].

There is also increasing evidence to show an association between infertility and adenomyosis [21]. Several mechanisms may be involved, including impairment of sperm transport [7], aberrant uterine contractility [22], alterations of adhesion molecules, cell proliferation, apoptosis, and free radical metabolism [15, 23]. Adenomyosis is also speculated to be a cause of recurrent implantation failure during IVF treatment [24].

6. Investigation

6.1. Two-Dimensional Ultrasound (USG). Two-dimensional (2D) transabdominal USG may reveal uterine enlargement or asymmetric thickening of the anterior and posterior myometrial walls. However, transabdominal USG is often not accurate enough in diagnosing adenomyosis as it fails to provide sufficient image resolution for visualization of the myometrium. Therefore, 2D transvaginal USG is often the first-line investigation. In a review performed by Reinhold et al., it was shown that transvaginal USG had a sensitivity of 80–86%, specificity of 50–96%, and an overall accuracy of 68–86% in diagnosing diffuse adenomyosis [25].

USG features of adenomyosis include the presence of three or more sonographic criteria: heterogeneity, increased echogenicity, decreased echogenicity, and anechoic lacunae or myometrial cysts [26]. In contrast to uterine fibroids, adenomyoma has a more elliptical shaped lesion with poorly defined borders, no calcifications, or edge shadowing. In

Table 2: Prevalence of adenomyosis from previous prospective cohort observational studies.

Study	Number of patients (n)	Study characteristics	Diagnostic modality	Definition of adenomyosis	Prevalence%
de Souza et al. 1995 [6]	26	Infertility patients presenting with dysmenorrhea or menorrhagia, all had laparoscopy performed	MRI	Focal adenomyoma: ill-defined lesions within the myometrium Diffuse adenomyosis: diffuse or irregular JZ thickening	54
Kunz et al. 2005 [7]	227	Study group (n = 160): infertility patients with laparoscopy done showing endometriosis Study subgroup: presence of endometriosis, <36 years old with fertile partners Control group (n = 67): infertility patients with no endometriosis or other pelvic disorder on laparoscopy	MRI	Focal adenomyoma: expansions of variable shape and size that did not extend over the whole length of the uterine cavity Diffuse adenomyosis: expansion of anterior or posterior JZ	79 90 28
Kissler et al. 2008 [8]	70	Patients with severe dysmenorrhea with laparoscopy performed Group I: patients with dysmenorrhea < 11 years Group II: patients with dysmenorrhea > 11 years	MRI	Maximal thickness >8 mm or greater on T2 weighted images	53 87
Naftalin et al. 2012 [9]	985	Consecutive patients attending the general gynaecology clinic	TVS	Asymmetrical myometrial thickening not caused by presence of fibroids, parallel shadowing, linear striations, myometrial cysts, hyperechoic islands, adenomyoma, and irregular JZ	21

MRI: magnetic resonance imaging; TVS: transvaginal ultrasound scan; JZ: junctional zone.

doubtful cases, Doppler sonography may be helpful in that blood vessels in the case of adenomyoma usually follow their normal vertical course in the myometrial areas while in the case of uterine fibroid, blood vessels are usually located in the periphery [27].

Sonographic diagnosis of adenomyosis is not always easy but the consensus statement and recommendation published by the MUSA (Morphological Uterus Sonographic Assessment) group on how sonographic features of adenomyosis should be described and measured should help to improve the diagnostic accuracy [28].

6.2. Three-Dimensional Ultrasound. Three-dimensional (3D) USG improves diagnostic accuracy of adenomyosis as it allows better imaging of the JZ [29]. The JZ is often visible as a hypoechogenic subendometrial halo which is composed of longitudinal and circular closely packed smooth muscle fibers. Upon 3D USG, adenomyosis is characterized by a thickened or irregular JZ [30]. Ahmadi and Haghighi showed the accuracy of 3D transvaginal USG in the diagnosis of adenomyosis to be 80% and a positive predictive value of 95% based on the detection of an irregular JZ on coronal plane [31]. Exacoustos et al. [30] analyzed a total of 72 premenopausal patients with 2D and 3D transvaginal USG before hysterectomy. In the study, the histological prevalence of adenomyosis was 44.4%. Their group agrees that the coronal section of the uterus obtained by 3D transvaginal USG allows accurate evaluation and measurement of the JZ and its alteration shows good diagnostic accuracy for adenomyosis. They showed that the presence of myometrial cysts was the most specific 2D transvaginal USG feature with specificity of 98% and accuracy of 78% while heterogeneous myometrium was the most sensitive feature with a sensitivity of 88% and accuracy of 75%. As for 3D transvaginal USG, with a JZ difference of more than or equal to 4 mm, JZ infiltration and distortion had a high sensitivity of 88% and the best accuracy of 85% and 82%, respectively. The overall accuracy of diagnosing adenomyosis for 2D and 3D transvaginal USG was 83% and 89%, sensitivity was 75% and 91%, specificity was 90% and 88%, positive predictive value was 86% and 85%, and negative predictive value was 82% and 92%, respectively. 3D USG also has the advantage of allowing storage of the images with subsequent offline manipulation and interpretation.

6.3. Magnetic Resonance Imaging. Magnetic resonance imaging (MRI) is the gold standard imaging modality for assessing the JZ in the evaluation of adenomyosis [32]. The common features of adenomyosis on MRI include (1) thickening of the JZ, JZ thickness $\geq$ 12 mm, or irregular junctional thickness with a difference of >5 mm between the maximum thickness and the minimum thickness, (2) an ill-defined area of low signal intensity in the myometrium on T2-weighted MR images, and (3) islands of ectopic endometrial tissue identified as punctate foci of high signal intensity on T1-weighted image [32–34]. However, MRI is expensive and may not be readily available in every unit. Moreover, Reinhold et al. [33] prospectively studied 119 patients undergoing hysterectomy and compared findings between TVS and MRI. The study showed that there was no significant difference in sensitivity and specificity between the two groups. Champaneria et al. [34] also performed a systematic review comparing test accuracy between USG and MRI for the diagnosis of adenomyosis. Their study findings are summarized in Table 3. They agreed that both TVS and MRI show high levels of accuracy for the noninvasive diagnosis of adenomyosis. However, we believe MRI may be particularly useful in the assessment of focal adenomyoma and provides important information on whether surgery should proceed.

Table 3: Accuracy of TVS and MRI for the noninvasive diagnosis of adenomyosis.

	TVS	MRI
Sensitivity	72%	77%
Specificity	81%	89%
Positive likelihood ratio	3.7	6.5
Negative likelihood ratio	0.3	0.2

TVS: transvaginal ultrasound scan; MRI: magnetic resonance imaging.

6.4. Shear Wave Elastography. A recent study also showed that using Aixplorer (Supersonic Imagine, France) scanner with application of shear wave elastography during transvaginal scanning may improve diagnostic accuracy of adenomyosis [35]. This study found that adenomyosis was associated with a significant increase of the myometrial stiffness estimated with shear wave elastography. Further studies are required to verify the clinical usefulness of such an approach.

6.5. Hysterosalpingography. Hysterosalpingography is seldom used to diagnose adenomyosis. However, in patients undergoing infertility assessment, the occasional finding of spiculations measuring 1–4 mm in length, arising from the endometrium towards the myometrium, or a uterus with the "tuba erecta" finding may be suggestive of adenomyosis [36].

6.6. Hysteroscopy. Several hysteroscopic appearances have been found to be associated with adenomyosis, including irregular endometrium with endometrial defects or superficial openings, hypervascularization, strawberry pattern, or cystic haemorrhagic lesions [37]. Nevertheless, there is limited data available on the diagnostic accuracy of these various features.

6.7. Hysteroscopic and Laparoscopic Myometrial Biopsy. In 1992, McCausland [38] showed that myometrial biopsy is helpful to diagnose adenomyosis. The study found that the depth of adenomyosis was correlated with the severity of menorrhagia. Of the 90 patients studied, 50 patients had normal hysteroscopy in which 55% of them had significant adenomyosis (greater than 1 mm) when compared to controls (0.8 mm). In that study, it was suggested that minimal adenomyosis may be treated definitively by endometrial ablation while deep adenomyosis should be treated by hysterectomy. They also showed that endometrial glands left under a scar could not only bleed and cause pain but also have malignant

potential. The authors suggested routine myometrial biopsy at the time of operative hysterectomy should be considered. However, Darwish et al. [39] showed hysteroscopic myometrial biopsies using rigid biopsy forceps to be inadequate and did not recommend its use. Popp et al. [40] showed that the sensitivity of a single myometrial biopsy in diagnosing adenomyosis ranged from 8 to 18.7%, while the specificity was 100% among 680 biopsy specimens in 68 surgically removed uterus using automatic cutting needle sampling. Gordts et al. [41] recommended the use of hysteroscopic guided biopsy for the diagnosis of adenomyosis using a new device, the Utero-Spirotome. It can also be used under ultrasound guidance to get access to small cystic adenomyoma lesions.

6.8. Laparoscopic Myometrial Biopsy. In a prospective, non-randomized study conducted by Jeng et al. [42] evaluating 100 patients with clinical signs and symptoms strongly suggestive of adenomyosis, the sensitivity of myometrial biopsy was 98% and the specificity 100%; the positive predictive value was 100% and the negative predictive value 80%, which were superior to those of transvaginal sonography, serum CA-125 determination, or the combination of both. The group suggested that laparoscopy-guided myometrial biopsy is a valuable tool in the diagnosis of diffuse adenomyosis in women presenting with infertility, dysmenorrhea, or chronic pelvic pain.

7. Management

As in the case of endometriosis, the management strategy of adenomyosis depends primarily on the presenting symptom and whether it is associated with reproductive failure.

7.1. Management of Menstrual Symptoms

7.1.1. Medical Treatment. Medical treatment for adenomyosis is similar to those given for endometriosis. Apart from symptomatic relief, hormonal treatment mainly works by inhibition of ovulation, cessation of menses, improving the hormonal milieu, and causing decidualization of the endometrial deposits.

Analgesic. Nonsteroidal anti-inflammatory drugs (NSAIDs) work by inhibiting the cyclooxygenase (COX-1 and COX-2) and decreasing the production of prostaglandins. NSAIDs have been proved to be effective in treatment of primary dysmenorrhea by Gambone et al. [43]. It is usually the first-line treatment for symptomatic pain relief for adenomyosis.

Oral Contraceptive Pills (OCPs). Combined oral contraceptive pills work by inhibiting ovulation by suppressing the release of gonadotrophins. Many studies have shown that they are effective in the treatment of dysmenorrhea. A prospective observational trial showed that continuous low-dose OCP were more effective than cyclical low-dose OCP in controlling symptoms in patients after surgical treatment for endometriosis [44]. Mansouri et al. [45] have shown regression of adenomyosis on MRI after using oral contraceptive pills for 3 years in adolescents with adenomyosis presenting with chronic pelvic pain.

Danazol. Danazol is an isoxazol derivative of 12 alpha-ethinyl testosterone. It causes a hypogonadic state and thus is widely used for treatment of endometriosis and abnormal uterine bleeding [46]. However, data on its use in adenomyosis remains limited. This may be due to its unwanted adverse effects after systemic treatment. In 2000, Igarashi et al. [47] reported a novel conservative medical therapy for uterine adenomyosis with a danazol-loaded intrauterine device in 14 women. During insertion of the danazol-loaded IUD, there was complete remission of dysmenorrhea in 9 patients, reduction in 4, and no change in 1 patient. There was complete remission of hypermenorrhea in 12 patients and no change in 2. Nine out of 14 patients also showed reduction in the maximum thickness of the myometrium as measured by MRI. However, further studies are required to confirm the clinical usefulness of the treatment.

Dienogest. Dienogest is a selective synthetic oral progestin that combines the pharmacological properties of 17-alpha-progesterone and 19 nor-progesterone with pronounced local effect on endometrial tissue. Dienogest has been shown to be effective in the treatment of endometriosis associated pelvic pain. A prospective clinical trial has shown dienogest to be a valuable alternative to depot triptorelin acetate for treatment of premenopausal pelvic pains in women with uterine adenomyosis. The study included a total of 41 patients with adenomyosis with pelvic pain and menorrhagia. The patients were allocated to receive oral dienogest (2 mg/day) or triptorelin acetate (3.75 mg/4 weeks) for 16 weeks. Both treatments were highly effective in treatment of dysmenorrhea, dyspareunia, and chronic pelvic pain associated with adenomyosis, although triptorelin acetate appeared superior to dienogest in controlling menorrhagia [48].

Levonorgestrel-Releasing Intrauterine Device (LNG-IUD). LNG-IUD is an intrauterine device, which release 20 micrograms of levonorgestrel per day. It has been shown to be an effective treatment for abnormal uterine bleeding. LNG-IUD acts locally and causes decidualization of the endometrium and adenomyotic deposits. LNG-IUD alleviates dysmenorrhea by improving uterine contractility and reducing local prostaglandin production within the endometrium. LNG-IUD appears to be an effective method in relieving dysmenorrhea associated with adenomyosis [49] and more effective than the combined OC pill [50], improved the quality of life [19], and appears to be a promising alternative treatment to hysterectomy.

LNG-IUD may be used in conjunction with other treatment modalities such as GnRH analogue [51] or transcervical resection of the endometrium (TCRE) [52]. In the latter study, it was found that TCRE combined with LNG-IUD was more effective in reducing menstrual flow compared with the LNG-IUD alone although there was no significant difference in the amount of pain reduction between the two treatment strategies.

GnRH Agonists. GnRH agonists are effective in alleviating dysmenorrhea and relieving menorrhagia associated with adenomyosis [53]. However, due to the undesirable

climacteric side effects and risk of osteoporosis, treatment with GnRH agonists is usually restricted to a short duration of 3–6 months although the duration of use may be extended if add-back estrogen therapy is employed [54]. Discontinuation of treatment usually leads to regrowth of the lesions and recurrence of symptoms.

Selective Estrogen Receptor Modulator (SERM). Selective estrogen receptor modulators like tamoxifen or raloxifene have been tried in the treatment of endometriosis [54] based on observations that SERMs may reduce endometriosis lesion in mouse [55]; however, their value in the treatment of adenomyoma has not been formally explored.

Aromatase Inhibitors. Like endometriosis, adenomyotic deposits are estrogen-dependent. Aromatase inhibitors inhibit the conversion of estrogen from androgens, thereby lowering the synthesis of estrogen. A prospective randomized controlled study found that the efficacy of aromatase inhibitors (letrozole 2.5 mg/day) in reducing the volume of adenomyoma as well as improving adenomyosis symptoms was similar to that of GnRH agonists (goserelin 3.6 mg/month) [56]. Kimura et al. also reported on the combined use of aromatase inhibitors with GnRH agonist with good results in a 34-year-old woman with severe uterine adenomyosis who wished to preserve fertility [57]. They found a reduction in uterine volume of 60% after 8 weeks of treatment as determined by magnetic resonance imaging and ultrasound.

Ulipristal Acetate. Ulipristal acetate (UPA) is a potent selective progesterone receptor modulator. There is good evidence to suggest that it can be used to shrink fibroid and control menorrhagia [58, 59]. It is possible that it may be similarly effective in the treatment of adenomyoma but literature data is lacking.

Antiplatelet Therapy. There is new evidence to suggest a role of antiplatelet therapy in treating adenomyosis. Emerging evidence suggests that endometriotic lesions are wounds undergoing repeated tissue injury and repair (ReTIAR), and platelets induce epithelial-mesenchymal transition (EMT) and fibroblast-to-myofibroblast transdifferentiation (FMT), leading ultimately to fibrosis. Adenomyotic lesions are thought to have similar pathogenesis to that of endometriosis. A recent study in mice suggests that antiplatelet treatment may suppress myometrial infiltration, improve generalized hyperalgesia, and reduce uterine hyperactivity [60].

7.1.2. Uterine Artery Embolization. Uterine artery embolization (UAE) has been used to treat symptomatic fibroids since the 1990s. There is increasing evidence to suggest that it is also effective in the treatment of management of adenomyosis. In a review of 15 studies including 511 women with adenomyosis, Popovic et al. found [61] significant clinical and symptomatic improvement in seventy-five percent of subjects at short- and long-term follow-up. A recent retrospective observational study of 252 patients who underwent UAE with up to five years of follow-up showed that improvement in dysmenorrhea and menorrhagia are more likely to occur in vascular lesions [62].

7.1.3. High Intensity Focused Ultrasound. High intensity focused ultrasound (HIFU) is another nonsurgical treatment for uterine fibroids that focuses high intensity ultrasound in the target lesion causing coagulative necrosis and shrinkage of the lesion. Both MRI and USG can be used for guidance for the procedure. MRI has better real time thermal mapping during the HIFU treatment. Yet, ultrasound guided HIFU is less costly and offers real time anatomic monitoring imaging and a grey scale change during treatment represents a reliable indicator in treatment response. It is effective in both focal and diffuse lesions [63, 64]. Ultrasound guided HIFU was shown to be technically successful in up to 94.6% of patients in a review of 2549 patients among 10 different centers with symptomatic adenomyosis [65].

7.1.4. Endomyometrial Ablation or Resection. There is limited report on the use of laparoscopic or hysteroscopic endometrial in treating adenomyosis in the literature. The success rate of myometrial electrocoagulation ranges from 55 to 70% as reported [66]. Wood [67] reported success in 4 out of 7 patients who underwent myometrial electrocoagulation, while Phillips et al. [68] had 7 out of 10 patients with symptomatic adenomyosis diagnosed by MRI treated with laparoscopic bipolar coagulation, having significant reduction or resolution of dysmenorrhea or heavy menstrual bleeding.

7.1.5. Hysterectomy. Hysterectomy is the definitive treatment option for intractable symptomatic adenomyosis when medical or other conservative treatments have failed to control the symptoms. Patients undergoing hysterectomy for adenomyosis should be advised of an increased risk of bladder injury and persistent pelvic pain. Furuhashi et al. [69] reviewed 1246 vaginal hysterectomies and found that patients undergoing vaginal hysterectomy for adenomyosis have increased risk of bladder injury compared with those performed for leiomyoma (2.3% versus 0.7%). It may be a result of difficulty in identifying the supravaginal septum and the vesicovaginal or vesicocervical planes. Several studies have reported on persistent pelvic pain after hysterectomy for adenomyosis [70]. Once a decision to proceed with hysterectomy has been made, the possibility of oophorectomy should be discussed. In general, it is not considered necessary to routinely remove the ovaries in premenopausal women [71, 72], but it may be indicated in women who suffer from cyclical symptoms, with concomitant ovarian endometriosis, or who are considered to have an increased risk of developing ovarian cancer, including those with a family history of the condition. Interestingly, a recent population-based study by Kok et al. [73] suggested that the risk of developing ovarian cancer in women with newly diagnosed adenomyosis is increased by 4-5-fold. If the finding is confirmed, there is a strong case to consider prophylactic oophorectomy at the time of hysterectomy for adenomyosis in premenopausal women.

7.2. Reproductive Failure. Several studies have shown that adenomyosis is associated with a negative impact on the success rate of IVF. In a recent meta-analysis conducted by Vercellini et al. [74], adenomyosis was associated with a 28% reduction in the likelihood of a clinical pregnancy in infertile women who underwent IVF/ICSI with autologous oocytes. Patients with adenomyosis were found to have higher chances of miscarriage, independent of oocyte or embryo quality. Thalluri and Tremellen [75] also showed that the adenomyosis was associated with a significant reduction in successful implantation of good-quality embryos in patients undergoing IVF treatment (viable clinical pregnancy rate 23.6% versus 44.6% among those who did not have adenomyosis, $P = 0.017$).

Puente et al. [76] performed a cross-sectional study of 1015 patients prior to assisted conception treatment. They found that the prevalence of adenomyosis was 24.4% in women aged ≥40 years and 22% in women aged ≤40 years. The prevalence of adenomyosis was found to be higher in those with recurrent pregnancy loss (38.2%) and previous ART failure (34.7%) when compared with those who did not (22.3% and 24.4%, respectively). They also found that 4 out of 5 patients had the diagnosis missed in earlier transvaginal ultrasonography.

The use of short-term GnRH agonists to shrink the size of the adenomyosis lesion has been shown to improve conception rate within 6 months of cessation of GnRH agonist therapy [77, 78].

In women with adenomyosis planning to undergo IVF treatment, the following management strategies should be considered.

7.2.1. GnRH Analogue Therapy before In Vitro Fertilization. Several studies have shown that pretreatment with GnRH analogue before IVF treatment improved pregnancy outcome. Zhou et al. [79] analyzed the clinical efficacy of leuprorelin acetate in treatment of uterine adenomyosis with infertility. They found that, after 2–6 months of leuprorelin acetate therapy, the mean uterine volume was significantly reduced from 180 ± 73 cm^3 to 86 ± 67 cm^3, leading to an improvement in embryo implantation and clinical pregnancy rates.

7.2.2. Stimulation Protocol. In women without pre-IVF GnRH analogue therapy as described above, long GnRH analogue protocol should be considered as it helps to induce decidualization of the adenomyotic deposits rendering the disease inactive. Tao et al. [80] showed that GnRH antagonist protocol appears to be inferior to GnRH agonist long protocol cycle, and the latter appeared to be associated with increased pregnancy and decreased miscarriage rates.

7.2.3. Two-Staged In Vitro Fertilization. In women with adenomyosis, a two-staged in vitro fertilization could be considered. Patients can undergo ovarian stimulation, oocyte retrieval, and fertilization followed by frozen-thawed embryo transfer (FET) at a later stage. Prior to the FET, GnRH analogue suppression therapy for 3 months or so leads to shrinkage of the adenomyosis. FET in the first HRT cycle following GnRH analogue suppression therapy, before the adenomyosis lesion regrows to its pretreatment size and exerts its adverse impact on implantation, may improve the result.

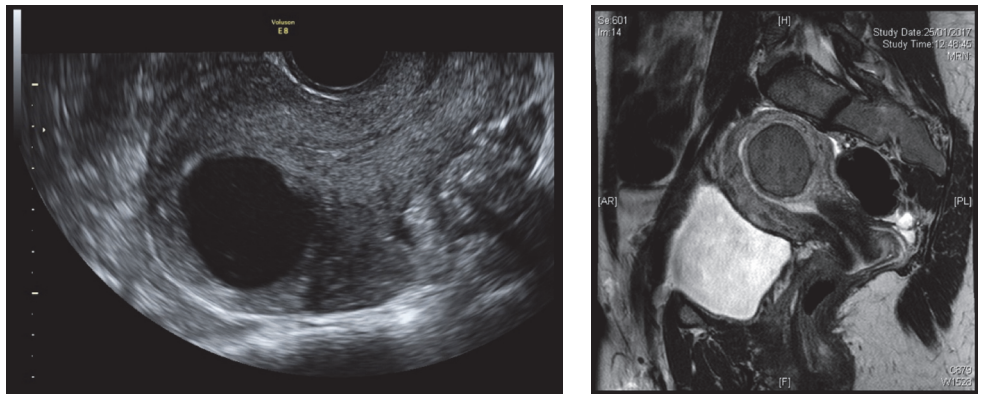
7.2.4. Mock Embryo Transfer. Performing a mock embryo transfer is desirable in women with adenomyosis, as it may help to assess the uterine cavity length and position, choose the correct transfer catheter, and alert the clinicians any extra precautions (e.g., use of tenaculum or cervical dilatation). Mock embryo transfer is particularly desirable in those with an enlarged uterus or distorted uterine cavity.

7.2.5. Single Embryo Transfer. Adenomyosis has been reported to be associated with increased incidence of preterm delivery, preeclampsia, and second trimester miscarriage when compared with the control group [81]. Consequently, multiple pregnancies should be avoided and so single embryo transfer should be advised. Women who had adenomyomectomy prior to IVF should also be advised to have SET to avoid multiple pregnancy with a view to minimize the risk of scar rupture.

7.2.6. HRT Protocol in Frozen-Thawed Embryo Transfer (FET) Cycle. GnRH agonist pretreatment to suppress the pituitary ovarian axis prior to hormone replacement therapy to prepare the endometrium in FET cycles appeared to improve the outcome compared with hormone replacement therapy without downregulation. In a study including 339 patients with adenomyosis, 194 received long-term GnRH agonist plus HRT (downregulation + HRT) and 145 with HRT alone. The clinical pregnancy, implantation, and ongoing pregnancy rates in the downregulation and HRT group were significantly higher than that of the HRT alone group, being 51.35% versus 24.83%, 32.56% versus 16.07%, and 48.91% versus 21.38%, respectively [82].

7.2.7. Uterine Contractility and Atosiban Therapy. Several functional studies showed that excessive uterine contractility (>5 contractions per minute) has been demonstrated in approximately 30% of patients undergoing embryo transfer and this may have a significant adverse impact on subsequent embryo implantation and clinical pregnancy rates [83]. The incidence of abnormal contractility appeared to be higher in women with adenomyosis [84] which may in part explain the higher incidence of reproductive failure observed in this group of women. Although recent evidence suggests that the routine use of atosiban therapy does not improve the outcome [85], it is possible that the use of atosiban in a selected group of women with aberrant uterine contractions during embryo transfer may improve the outcome. Ideally, women with adenomyosis should be screened for abnormal uterine contractions during ET; if the results are abnormal atosiban therapy should be discussed; alternatively, the possibility of empirical atosiban therapy in women with adenomyosis and recurrent implantation failure could be considered.

7.2.8. Recurrent Implantation Failure. Recurrent implantation failure is diagnosed when there is failure to achieve a



(a) (b)

Figure 1: (a) Ultrasound and (b) MRI appearance of a cystic adenomyoma.

clinical pregnancy after transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles in a woman under the age of 40 years [86]. It is known that adenomyosis is associated with recurrent implantation failure [24]. Women with recurrent implantation failure should be offered 3D scan or MRI to establish if there is adenomyosis; if adenomyosis is present, the above management strategies should be adopted to improve the outcome.

7.2.9. Uterine Sparing Conservative Surgery. Surgery is seldom required for women prior to IVF treatment, the indication being (1) well-defined adenomyoma more than 5 cm and (2) recurrent miscarriage or recurrent implantation failure after IVF. A retrospective cohort study performed by Kishi et al. [87] involving 102 women showed that laparoscopic adenomyomectomy was beneficial for women who experienced IVF treatment failures if they were <39 years old but not for patients aged 40 years or more. No benefit of uterine sparing surgery is seen for those older patients aged 40 or above. Grimbizis et al. [88] reviewed the current literature and described three main categories of uterine sparing surgical treatment, including complete excision by adenomyomectomy; cystectomy or partial excision cytoreductive surgery; and nonexcisional techniques including uterine artery ligation, electrocoagulation of myometrium, resection, and ablation. The review concluded that uterine sparing treatment of adenomyosis appears feasible and effective. After complete excision, the dysmenorrhea reduction, menorrhagia control, and pregnancy rate were 82.0%, 68.8%, and 60.5%, respectively. After partial excision, the dysmenorrhea reduction rate was similar at 81.8%, although menorrhagia control and pregnancy rate were slightly reduced to 50.0% and 46.9%, respectively.

7.3. Hysteroscopic Surgery. Just as it is now possible to remove intramural myoma with refined hysteroscopic techniques, hysteroscopic adenomyomectomy may also be possible in selected cases, especially when the adenomyoma is <5 cm or when it protrudes into the uterine cavity. However, hysteroscopic adenomyomectomy should always be carried out under USG guidance. A minimal safety margin of 5 mm between the serosa and adenomyoma is considered necessary to avoid the risk of uterine perforation although the safety margin may sometimes increase after part of the lesion has been removed and the uterine contractions which follow help to push the adenomyoma further towards the cavity. Pretreatment with 3-month course of GnRH agonist beforehand can help reduce the vascularity and bleeding during the operation. Sometimes, it may also help to push the adenomyoma towards the uterine cavity due to the reduction of uterine volume.

The location of the adenomyoma should be clearly defined before the start of the procedure. Using a lower perfusing pressure, say at 40 mmHg instead of the usual 90–100 mmHg, may allow a slight bulge of the adenomyoma into the cavity to be visualized. Vasopressin, a potent vasoconstrictor, may be injected into the uterus by using an oocyte retrieval needle [89] to result in contraction of the uterus and reduce bleeding. Afterwards the endometrium and the myometrium overlying the adenomyoma can be incised using a cutting loop or needle or dissected with the use of a pair of scissors, following which the adenomyoma is removed by the cutting loop or a pair of grasping forceps coupled with twisting actions, separating it from the underlying myometrium. The latter step may be achieved with the use of Hysteroscopy Endo-Operative System (HEOS) [90], which allows both mechanical and electrosurgical instruments to be used. Complete removal of the adenomyoma may be difficult. A repeat surgical procedure may be required from time to time.

Cystic adenomyoma is a special category of adenomyoma. Figures 1(a) and 1(b) show the ultrasound and MRI appearance of a cystic adenomyoma. At the beginning of the hysteroscopic operation, the adenomyoma did not appear to bulge into the cavity (Figure 2(a)), but upon lowering the perfusing pressure, the cystic adenomyoma was seen bulging into the cavity (Figure 2(b)), which permits the precise location of the lesion to be identified. In this particular case, a longitudinal incision was made over the adenomyoma, draining a large amount of blood clots from the cystic adenomyoma. In this case, initial attempts to dissect the cystic adenomyoma away from the myometrium (Figure 2(c)) had

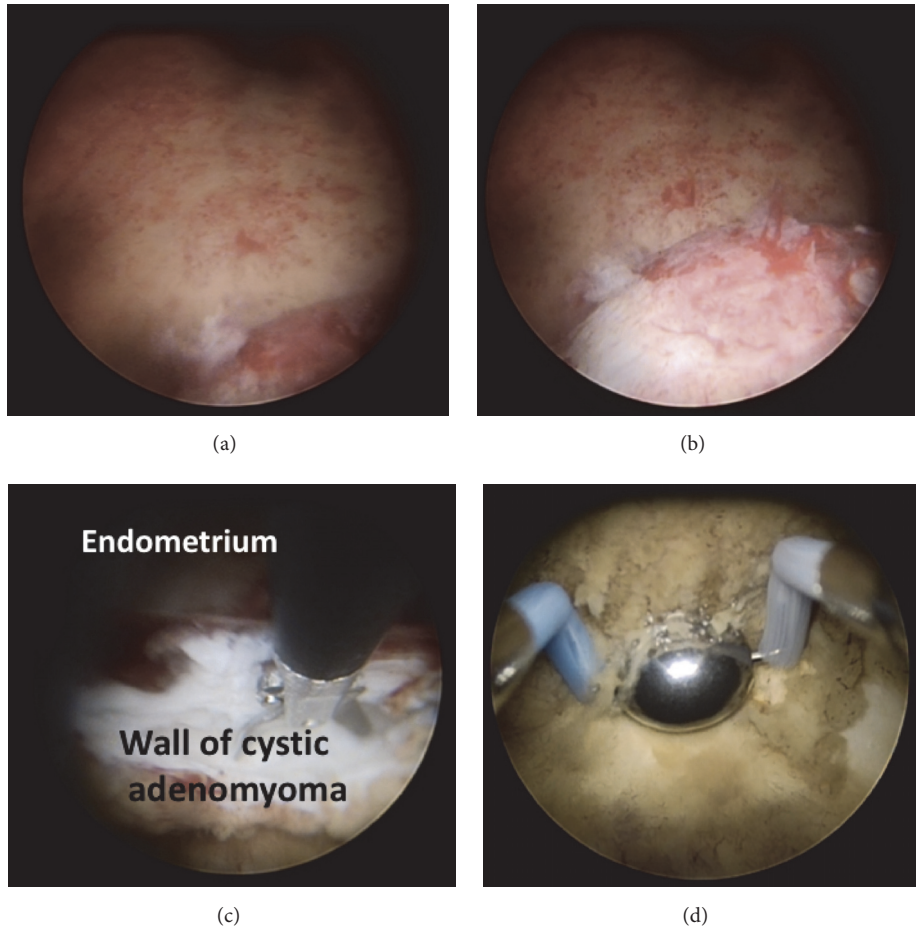


Figure 2: (a) Hysteroscopic view at high perfusion pressure. (b) Hysteroscopic view at low perfusion pressure with bulging of cystic adenoma seen. (c) Hysteroscopic dissection of cystic adenomyoma wall away from endometrium. (d) Roller ball ablation of adenomyotic deposits.

to be abandoned because the lesion was too firmly adherent to the myometrium, without a well-defined cleavage plane, in contrast to the situation of a myoma. Consequently, the cyst wall, including the yellow-brown deposits representing the ectopic endometriotic deposits (Figure 2(d)), was ablated under ultrasound guidance with the use of a roller ball diathermy.

8. Conclusion

Many treatment modalities are now available for the treatment of adenomyosis. The management plan ought to be individualized, depending on the presenting symptom and the desire to achieve a successful pregnancy. Recent development in various nonsurgical and surgical options has significantly improved the prospect of a successful treatment in women wishing to conceive again.

Conflicts of Interest

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

Authors' Contributions

Jin-Jiao Li and Jacqueline P. W. Chung contributed equally to the manuscript.

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Review Article

A Comprehensive Review of the Pharmacologic Management of Uterine Leiomyoma

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Uterine leiomyomata are the most common benign tumors of the gynecologic tract impacting up to 80% of women by 50 years of age. It is well established that these tumors are the leading cause for hysterectomy with an estimated total financial burden greater than $30 billion per year in the United States. However, for the woman who desires future fertility or is a poor surgical candidate, definitive management with hysterectomy is not an optimal management plan. Typical gynecologic symptoms of leiomyoma include infertility, abnormal uterine bleeding (AUB)/heavy menstrual bleeding (HMB) and/or intermenstrual bleeding (IMB) with resulting iron-deficiency anemia, pelvic pressure and pain, urinary incontinence, and dysmenorrhea. The morbidity caused by these tumors is directly attributable to increases in tumor burden. Interestingly, leiomyoma cells within a tumor do not rapidly proliferate, but rather the increase in tumor size is secondary to production of an excessive, stable, and aberrant extracellular matrix (ECM) made of disorganized collagens and proteoglycans. As a result, medical management should induce leiomyoma cells toward dissolution of the extracellular matrix, as well as halting or inhibiting cellular proliferation. Herein, we review the current literature regarding the medical management of uterine leiomyoma.

1. Introduction: Uterine Leiomyomata

Uterine leiomyomata, also referred to as myomas and fibroids, are the most common solid tumors of the gynecologic tract. These benign tumors are postulated to arise from a single, genetically altered, mesenchymal cell under the influence of gonadal hormones, namely, progesterone and 17β-estradiol. Epidemiologic data report that leiomyomata are virtually nonexistent prior to menarche and typically have an indolent course following menopause, strongly implicating gonadal hormones in the induction and maintenance of this disease process [1]. These benign tumors are found in 70% of women of European descent and more than 80% of women of African descent by 50 years of age [2–7]. Despite the high percentage of women affected by leiomyomata, it has been estimated that only 20%–30% will become symptomatic of their disease [8, 9]. Risk factors for the development of the disease have been identified and include increasing age, nulliparity, obesity, premenopausal status, personal history of hypertension, family history, race/ethnicity, time since last birth, and consumption of food additives and soybean milk [10, 11]. Of note, the strongest epidemiologic correlate is increasing age followed by a woman's race/ethnic background. To this end, women of African descent are at increased risk of developing multiple and larger leiomyomata at younger ages than their white counterparts [5].

Increasing tumor burden results in characteristic symptoms depending on the location of the tumor within the uterine corpus, that is, whether the tumor is submucosal, intramural, or subserosal. For example, leiomyomata distorting the uterine cavity (submucosal and intramural) often produce abnormal uterine bleeding (AUB), heavy menstrual

bleeding (HMB), and/or intermenstrual bleeding (IMB) in the presence or absence of dysmenorrhea. These cavity-distorting tumors are often implicated in iron-deficiency anemia (secondary to AUB) and infertility. If a given patient is able to achieve pregnancy with a leiomyoma impacting the uterine cavity, they also are more likely to experience adverse pregnancy outcomes to include recurrent pregnancy loss (RPL), abnormal placentation (i.e., placenta previa), fetal malpresentation, preterm delivery, cesarean section, and postpartum hemorrhage [12–14]. Tumors in other locations, namely, intramural (well separated from the uterine cavity) and subserosal subtypes, are more often associated with pelvic pressure, pelvic pain, dyspareunia, chronic constipation, and urinary incontinence.

Hysterectomy is one of the most common surgeries performed on women and remains the only definitive treatment for leiomyomata. Myomectomy provides temporary reduction in uterine volume but is associated with a risk of recurrence estimated to be 11% with removal of a solitary fibroid and 26% or greater when multiple fibroids are removed over a 10–30-month time period [14, 15]. The failure of minimally invasive surgery to resolve disease contributes to more than 600,000 hysterectomies per year in the United States [16–18]. Estimates place the annual direct cost for surgery, hospital admissions, outpatient visits, and medications to be as high as $9.4 billion per year [19, 20]. However, when considering lost work time and hospital fees associated with poor obstetric outcomes, the economic burden of leiomyomata on the United States healthcare system is estimated to reach beyond $30 billion [20].

Multiple less invasive techniques including hysteroscopic myomectomy (used for submucosal fibroids), magnetic resonance imaging-guided focused ultrasound surgery, cryomyolysis, uterine artery embolization, and temporary occlusion of the uterine arteries have been employed to offer uterus-sparing options [21]. However, the safety and efficacy for use in women desiring future fertility have not been thoroughly defined for each of these less invasive procedures. In addition to the aforementioned therapeutic options, multiple medications have been employed to provide alternatives to hysterectomy. Despite the availability of such noninvasive therapies, current literature has not shown a definitive reduction in the numbers of hysterectomies performed in the United States given that most medical therapies result in a rapid return of symptoms and/or tumor volume with cessation of treatment [16, 17, 22, 23].

Because gonadal hormones induce, and maintain, leiomyoma growth via the production of an aberrant extracellular matrix (ECM), much research has focused on the development of medical agents to circumvent steroidal influence in an effort to reduce the burden of disease. These medications include centrally acting gonadotropin-releasing hormone analogs (leuprolide acetate, cetrorelix) and peripherally acting agents to include aromatase inhibitors, antiprogestins, and selective progesterone receptor modulators (SPRMs).

Taken together, the management of leiomyoma depends on given patient's symptoms, age, and desire for future fertility. In the case of women suffering from abnormal uterine bleeding, heavy menstrual bleeding, medical management with NSAIDs, progestin, combination of oral contraceptives, a levonorgestrel releasing intrauterine device, or tranexamic acid has been shown to be beneficial [24]. On the other hand, anatomic lesions causing abnormal uterine bleeding, such as uterine leiomyoma or polyps, may necessitate surgical intervention. Endometrial ablation and resection are minimally invasive surgical options to control abnormal uterine bleeding, heavy menstrual bleeding, in women with a normal uterine cavity who have completed childbearing. Women with small submucosal fibroids may also consider endometrial ablation for management of bothersome heavy menstrual bleeding. Despite the less invasive technique, patient satisfaction is not guaranteed. In fact, 27% of women who undergo endometrial ablation proceed with additional surgical interventions to include hysterectomy [17, 25]. Furthermore, patient symptoms and satisfaction are equally improved with the use of progesterone releasing intrauterine devices and endometrial ablation [26, 27].

For those women either not interested in definitive management with hysterectomy or considered to be poor surgical candidates, options for management of their disease should include agents aimed at reducing tumor burden by dissolution of the aberrant ECM. Herein, this manuscript will review the medical management of symptomatic uterine leiomyomata with particular emphasis placed on those medications that favor dissolution of the aberrant ECM.

2. Nonhormonal

2.1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). Nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, and mefenamic acid) have been employed in an effort to ameliorate abnormal uterine bleeding/heavy menstrual bleeding for a number of years. These agents inhibit the enzyme cyclooxygenase, which diminishes the production of prostaglandins. A Cochrane review evaluating the effectiveness of NSAIDs in the management of abnormal uterine bleeding/heavy menstrual bleeding included 18 studies [28]. The authors found the use of NSAIDs was superior to placebo but less effective than tranexamic acid, danazol, or the levonorgestrel releasing intrauterine device when evaluating the therapeutic impact on abnormal uterine bleeding [28]. Despite their usefulness with reducing both dysmenorrhea and blood loss, these agents have not been shown to lead to dissolution of the leiomyoma ECM.

2.2. Tranexamic Acid. Tranexamic acid is a synthetic lysine derivative that prevents fibrin degradation by competitively blocking lysine-binding sites on plasminogen, thereby preventing fibrin degradation. This action favors clotting, which reduces menstrual blood flow. Several randomized control trials have demonstrated a reduction in menstrual blood flow as compared to placebo [29–31]. Tranexamic acid was approved by the FDA in 2009 for the treatment of women suffering from abnormal uterine bleeding/heavy menstrual bleeding secondary to ovulatory disorders, not uterine leiomyoma.

Several studies have specifically evaluated the impact of tranexamic acid on women with symptomatic uterine leiomyomata [29–31]. In these studies, its utility in improving blood loss is not well established. Furthermore, these studies revealed an increased risk of necrosis and infarction of the leiomyoma, which could lead to pain and provide a potential site for infection. Despite the theoretical benefit in women with uterine leiomyomata, tranexamic acid has no effect on the ECM and reducing the burden of disease.

3. Hormonal Therapy

The steroid hormones 17β-estradiol and progesterone, in combination or progesterone only formulations, are commonly utilized to regulate heavy menstrual bleeding in women with and without uterine leiomyoma. Strict regulation of the menstrual cycle via these medications is particularly beneficial in women suffering from anovulation. Despite the aforementioned benefits, current evidence suggests medical therapies provide short-term relief, with many patients ultimately opting to pursue surgical therapies [32, 33].

3.1. Combined Oral Contraceptives. Given our current understanding of the importance of the gonadal hormones for initiation and continued growth of uterine leiomyomata, many physicians previously recommended against the use of such medications in women with uterine leiomyomata. Despite these fears, combined oral contraceptives have been utilized for women with leiomyomata and a meta-analysis found no association with progression of disease while using these medications [34]. In fact, this study found the risk of uterine leiomyomata associated morbidity was reduced by 17% in those who used combined oral contraceptives for 5 or more years.

The current data are limited regarding the effects of estrogen and progesterone. Estrogen and progesterone treatment, usually with combined oral contraceptive pills, may control abnormal uterine bleeding (by suppressing endometrial growth) and may not stimulate leiomyoma ECM.

3.2. Progesterone. Progesterone containing oral, injectable, and implantable contraceptives act to reduce blood loss by providing an inhibitory effect on endometrial cell proliferation leading to a thinner lining with less material to be shed during progestin withdrawal. However, as was the case with combined oral contraceptives, studies utilizing progesterone only contraceptives in the treatment of symptomatic uterine leiomyomata have demonstrated mixed results. To this point, there are studies in which the authors note reduction in leiomyomata size with progesterone only therapy, while others report an increase in leiomyomata size [35–38]. A well-designed, randomized controlled trial is needed to adequately study the effects of exogenous progestin in the treatment of women with uterine leiomyomata.

3.3. Levonorgestrel Releasing Intrauterine Device (LNG-IUD). The levonorgestrel releasing intrauterine device (LNG-IUD) acts at the level of the endometrium to repress estrogenic stimulated growth thereby producing a thinned endometrial lining. In addition, there is virtually no uptake of levonorgestrel into the systemic circulation [33].

Progestin releasing intrauterine devices are effective at treating abnormal uterine bleeding associated with anovulation and is now approved by the Food and Drug Administration for this indication [33]. Small studies suggest the LNG-IUD may be effective for treatment of abnormal uterine bleeding/heavy menstrual bleeding in women with leiomyoma; however, no randomized controlled trials have been performed using this patient population [39].

4. Aromatase Inhibitors

Aromatase (CYP19) is an enzyme responsible for ovarian and peripheral conversion of androgens, namely, testosterone, to 17β-estradiol. Several *in vitro* studies revealed that uterine leiomyoma cells harbor intrinsic aromatase activity, thereby providing a direct source of steroid hormone to drive further growth through the development of an aberrant extracellular matrix [40]. This finding stimulated interest in the utilization of aromatase inhibitors as pharmacologic agents in the treatment of leiomyomata.

Based on their mechanism of action, aromatase inhibitors were hypothesized to have fewer side effects than the GnRH agonist, leuprolide acetate, with the benefit of a rapid effect. Several publications have shown reductions in leiomyomata volume and symptoms with the use of these agents [41–45].

One study using the aromatase inhibitor, CGS 20267, revealed the ability of that agent to inhibit ovarian and peripheral conversion of androgens to 17β-estradiol within 24 hours of first use [41]. A small open-label trial involving twenty patients evaluated the effects of a second aromatase inhibitor, anastrozole, on uterine volume without changes in circulating FSH or 17β-estradiol levels [46]. A subsequent randomized controlled trial compared letrozole, an aromatase inhibitor, against triptorelin, a GnRH analog [42]. The study ultimately found reductions (45% versus 33%, resp.) in tumor burden; however women in the letrozole-arm experienced fewer side effects and avoided symptoms associated with the initial GnRH flare.

A Cochrane review published in 2013 on aromatase inhibitors used for the management of uterine leiomyomas focused on one randomized control trial with 70 patients that met inclusion criteria [47]. The authors concluded there was insufficient evidence to support the use of aromatase inhibitors in the treatment of women with uterine fibroids [47]. In the absence of well-designed trials, these agents have yet to be approved by the United States Food and Drug Administration (FDA) for use in women with uterine leiomyomata.

5. Gonadotropin-Releasing Hormone Analogs

5.1. GnRH Agonist. In normal human physiology, sex steroid hormone production is a highly regulated process with major control centering at the hypothalamus, which is below the third ventricle and directly above the chiasma and pituitary

gland. This gland exerts control over sex steroid production via the release of gonadotropin-releasing hormone (GnRH). When released in a specific, pulsatile fashion, GnRH induces the release of the pituitary gonadotropins Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH), which in turn act at the level of the ovary to stimulate production of the sex-steroids, 17β-estradiol, and progesterone, respectively. Compounds that regulate ovarian stimulation and thereby decrease gonadal hormone production are attractive treatment options for women suffering from gonadal hormone-stimulated diseases such as leiomyomas.

As a class of medication, GnRH agonist (leuprolide acetate, goserelin acetate, and nafarelin acetate) has historically been considered the most effective presurgical therapy for symptomatic leiomyoma. They induce a premenarchal state notable for hypoestrogenism, by downregulation of the hypothalamic-pituitary-ovarian axis, amenorrhea, improvement in symptoms (namely, AUB-HMB/IMB), and rapid reduction in leiomyomata volume. That being said, the benefits achieved come with an unavoidable side effect profile to include vasomotor symptoms, vaginal dryness, sleep disturbances, myalgia, arthralgia, mood-swings, and potential cognitive impairment [33, 48, 49]. Long-term therapy, greater than 6 months, with GnRH agonists has been implicated in bone loss of approximately 6% [50]. Important to note, the benefits, and side effects, of GnRH agonists are temporary and reverse with the discontinuation of the medication [33, 49–52].

In one of the large scale clinical trials assessing leuprolide efficacy in women with symptomatic leiomyomata, 128 women were enrolled and placed into either the treatment or placebo arm [51]. Those in the treatment arm received 3.75 mg leuprolide acetate intramuscularly monthly for a total of 6 months. The authors found a 36% reduction in uterine volume at 12 weeks and 45% with 24 weeks of treatment. However, mean uterine volume returned to pretreatment size 24 weeks after cessation of leuprolide acetate [51].

Similar studies have been performed and produced similar results with all showing a 30–65% reduction of leiomyomata within 6 months of treatment with leuprolide acetate [51–55]. However, given the hypoestrogenic state and bone loss, most organizations including the American Congress of Obstetricians and Gynecologist (ACOG) recommend limiting the use of leuprolide acetate to symptomatic women scheduled to undergo surgery within 6 months of initiating therapy [33, 49]. If used longer, ACOG recommends that low-dose steroidal add-back therapy be considered to minimize continued bone loss and vasomotor symptoms. To this end, leuprolide acetate has been approved by the United States Food and Drug Administration for preoperative therapy in woman with iron-deficiency anemia secondary to leiomyomata.

On a molecular level, GnRH agonists decrease the expression of factors important for fibroid growth to include Transforming Growth Factor-Beta, Epidermal Growth Factor, and Insulin-like Growth Factor. Further data from our laboratory has shown reduction of the extracellular components collagen -1, fibronectin, and versican with leuprolide acetate treatment [56, 57].

5.2. GnRH Antagonist. Similar to the GnRH agonists, GnRH antagonists including cetrorelix acetate, ganirelix acetate, and Nal-Glu have been shown in clinical trials to reduce leiomyoma volume via induction of a hypoestrogenic state [58–62]. However, these medications are injected and must be taken every 1 to 4 days because there are currently no long-acting depot forms available in the United States, which limits their usefulness with regard to the medical treatment of leiomyomata.

5.3. Antiprogestins. Progesterone receptor A and B (PR-A, PR-B) protein has been shown to be elevated within leiomyomata, as compared against adjacent myometrium [63, 64]. Additional publications have directly implicated progesterone action via PR-A and PR-B with the production of an aberrant extracellular matrix. Taken together, these points make inhibitors of the PR an area of interest for the medical management of leiomyomata.

Mifepristone, also known as RU 38486 & RU486, is the most extensively studied progesterone receptor antagonist in leiomyomata [65–69]. This compound is a competitive antagonist and has higher infinity for the ligand-binding domain of the PR than does progesterone [70, 71]. Several studies have shown mifepristone is capable of improving symptoms and reducing the volume of leiomyomata [65, 66, 72–74]. One study compared increasing doses of mifepristone in 40 premenopausal women with symptomatic leiomyomata [66]. Study participants took either 5 or 10 mg of mifepristone daily for one year and were followed with serial imaging. Ultimately, the authors found a reduction in uterine volume of 48% after 6 months of treatment and 52% after one year. Amenorrhea occurred in 65% at 6 months and 70% at one year. Although encouraging, there were 6 cases of simple endometrial hyperplasia without atypia in the 10 mg group. A subset of study participants was followed for an average of 6 months at the completion of the study and most had modest reenlargement of their leiomyomata.

A Cochrane review evaluated the usefulness of mifepristone for symptomatic leiomyomata [72]. Of all studies on this topic, 3 randomized controlled trials with a total of 112 patients with symptomatic leiomyomata met inclusion criteria [65, 73, 74]. The review concluded mifepristone indeed reduced abnormal uterine bleeding-heavy menstrual bleeding/intermenstrual bleeding, and also improved fibroid-specific quality of life. Despite the aforementioned improvements, the Cochran review found no significant reduction in leiomyomata volume with mifepristone therapy.

Overall, the weight of the evidence suggests that treatment with mifepristone leads to a reduction in patient symptoms associated with leiomyomata that is comparable to GnRH analogs without detrimental effects on bone mineral density. However, given the unopposed estrogen stimulation of the endometrium with development of endometrial hyperplasia, caution must be taken given the potential for development of estrogen-dependent endometrial cancers. It is for this reason that approval has not been sought from the Food and Drug Administration for use of these medications in women with symptomatic leiomyomata.

6. Selective Progesterone Receptor Modulators (SPRMs)

Selective progesterone receptor modulators (SPRMs) are a class of medications that are structurally similar to the antiprogestin mifepristone. Similar to the more widely known Selective Estrogen Receptor Modulators (SERMs), SPRMs have tissue-specific agonist and antagonist effects making them prime agents for use in the treatment of uterine leiomyomata. Members of this class of medication include telapristone acetate (also known as CDB-4124), asoprisnil (also known as J867), and ulipristal acetate (also known as CDB-2914).

Asoprisnil (J867) was originally developed by Schering and TAP Pharmaceutical Products in the mid to late 1990s [75]. The major metabolite of the drug, J912, was shown to have high-binding affinity for the progesterone receptor, moderate affinity for glucocorticoid receptor, low affinity for androgen receptor, and no binding affinity for estrogen or mineralocorticoid receptors. Because of its promising *in* vitro and animal work, the drug went to clinical trial for treatment of symptomatic uterine fibroids in humans. These *in vitro* models have shown that asoprisnil downregulates growth factors and synthesis of collagens, which are important in increasing leiomyoma, bulk [76, 77]. Despite these promising attributes, phase III clinical trials were halted secondary to concerning progesterone receptor-modulator associated endometrial changes (PAECs). The histologic changes associated with PAECs are dilated, weakly secretory endometrial glands with mitotic figures, and stromal effects ranging from compaction to nonuniform edema [78–80]. A panel of gynecologic pathologists examined these changes and concluded they should not be considered a safety concern [81].

Telapristone acetate (CDB-4124) was developed at the National Institutes of Health, Contraception Development Branch [82]. The phase III, open-label, parallel, randomized, multicenter study was halted in 2009 after patients were found to have significant elevations in their liver function tests (LFTs), suggesting hepatotoxicity.

Similar to telapristone acetate, ulipristal acetate (CDB-2914) was developed by the National Institutes of Health, Contraception Development Branch. This drug was made available as an emergency form of contraception in Europe in 2009 and subsequently approved in the United States in 2010 [83]. In this capacity, 30 mg of ulipristal acetate has been shown to be effective up to 5 days after unprotected intercourse [84].

Given the enthusiasm for the use of SPRMs in the management of leiomyoma, a group at the National Institutes of Health (NIH), National Institute of Child Health and Disease Branch (NICHD), performed a randomized control trial including 22 premenopausal women with symptomatic uterine leiomyomata [85, 86]. Women were assigned into one of three arms: CDB-2914 10 mg, CDB-2914 20 mg, or placebo for the equivalent of 3 menstrual cycles. The authors found a significant reduction in leiomyomata volume by an average of 21% (10 mg arm) and 36% (20 mg arm) after 3 months of treatment. Moreover, patients experienced an improvement in symptoms based on the Uterine Fibroid Symptom Quality of Life assessment. The same group published a second, randomized, double-blind, placebo-controlled, phase IIb study in 42 premenopausal women in which symptomatic uterine leiomyomata were randomized to receive placebo, CBD-2914 10 mg, or 20 mg for 12 weeks (treatment 1). A second 12-week treatment with CDB-2914 was offered. Again, the authors found significant improvements in abnormal uterine bleeding, quality of life, and leiomyomata volume at 3 and 6 months of treatment [86].

Subsequent to the NIH trials, a European group evaluated the ability of ulipristal acetate to reduce symptoms and tumor burden in symptomatic uterine leiomyomata. The PGL4001 (ulipristal acetate) Efficacy Assessment in Reduction of symptoms due to uterine Leiomyoma (PEARL) I trial compared ulipristal acetate to placebo in the preoperative management of 242 premenopausal women suffering from symptomatic leiomyomata [87]. The authors concluded that treatment with ulipristal acetate for 13 weeks controlled bleeding in 91% of women receiving 5 mg, 92% of women receiving 10 mg, as compared to 19% of those receiving placebo. There was 21% and 12% reduction of leiomyomata volume in those receiving 5 mg and 10 mg, respectively.

The authors of the PEARL I trial then performed a noninferiority trial comparing ulipristal acetate (5 mg and 10 mg) to leuprolide acetate [88]. The study included 307 premenopausal women with symptomatic leiomyomata. Following a 3-month treatment 90% of patients in the 5 mg arm and 98% in the 10 mg arm had control of bleeding, as compared to 89% in the leuprolide acetate group. Leiomyomata volume was found to have decreased by 36%, 42%, and 53%, respectively.

The leaders of the European group subsequently performed a third clinical trial with repeated intermittent open-label UPA courses, each followed by randomized double-blind norethisterone acetate (NETA) or placebo including 291 premenopausal women with symptomatic leiomyomata. The authors found the median fibroid volume change from baseline was −63%, −67%, and −72% after treatment courses 2, 3, and 4, respectively. The authors conclude that repeat courses of ulipristal acetate control symptoms and significantly reduce leiomyoma volume [89].

Taken together, the PEARL trials provided sufficient evidence for the regulatory agencies of the European Union to approve ulipristal acetate as a preoperative treatment of symptomatic leiomyomata. To date, there are insufficient studies in the United States and therefore the Food and Drug Administration has not approved ulipristal for use in symptomatic uterine leiomyoma.

Similar to antiprogestins that inhibit progesterone activity in the endometrium, leading to unopposed estrogen stimulation with the potential development of endometrial intraepithelial neoplasia leading to Type I endometrial cancers, many have concerns regarding the long-term treatment of patients with ulipristal acetate. In one early study evaluating CBD-2914 as a contraceptive, 56 normally cycling women were treated with a single dose of ulipristal acetate (10 mg, 50 mg, or 100 mg) or placebo within 48 hours of ovulation and followed with transvaginal ultrasound (to evaluate endometrial

thickness) and endometrial sampling (to evaluate potential changes within the endometrium). Of the 56 endometrial biopsies performed, one patient who received 50 mg of ulipristal acetate was noted to have findings consistent with benign endometrial intraepithelial neoplasia. Repeat luteal phase endometrial sampling performed two months later was negative for pathologic endometrial changes [90]. A single case report discussed a patient with benign metastatic leiomyoma who was treated with ulipristal acetate for 5 years continuously. The authors performed regular endometrial sampling over the patient's treatment course and found no evidence of endometrial intraepithelial neoplasia or progesterone receptor-modulator associated changes (PRACs), suggesting long-term therapy with this ulipristal acetate may be safe from an endometrial standpoint. A more recent systematic review evaluating the effects of SPRMs on the endometrium evaluated 1450 treated with ulipristal acetate [91]. The authors found 6 cases of endometrial pathology in women undergoing or previously treated with ulipristal acetate. Five women were diagnosed with benign endometrial intraepithelial neoplasia (previously called simple or complex hyperplasia without atypia) and one case of endometrial intraepithelial neoplasia (formerly referred to as simple or complex hyperplasia with atypia). The single case of EIN resolved spontaneously during treatment. The authors found no cases of endometrial cancer during or after treatment with ulipristal.

Our laboratory performed an RNA sequence (RNAseq) analysis on placebo and ulipristal acetate treated patient matched leiomyoma and normal myometrium samples from the ulipristal (CBD-2914) clinical trials in an effort to identify novel pathways involved in the UPA-dependent reduction of uterine leiomyoma [85, 86]. Interesting observations from this set of experiments were alterations in the profibrotic, Transforming Growth Factor-β3 (TGF-β3) signaling pathway. First, the RNAseq data revealed a marked increase in Fibrillin transcripts in UPA-treated leiomyoma, as compared to placebo (Figure 1). Fibrillin is known to attenuate TGF-β3 signaling. Furthermore, there was a reduction in TGFRI, TGFRII, and TGF-β3 transcripts in UPA-treated leiomyoma. These findings were confirmed in proteomic studies utilizing both Western immunoblotting on proteins extracted from the study tissue and also immunohistochemistry on tissue (Figure 2).

The most significant changes in transcript levels were seen in those coding for the proteoglycan, versican (VCAN). This molecule is negatively charged, with large numbers of hydrophilic glycan components that form high-molecular weight aggregates with hyaluronic acid. Because of its structure, VCAN promotes hydrostatic pressure within the interstitial space. Therefore, reductions in VCAN would, in theory, lead to dehydration of uterine leiomyoma. Our analysis of the RNAseq study revealed VCAN transcripts were 4–6 times higher in leiomyoma than surrounding myometrium (data not shown). Furthermore, mRNA transcripts and protein expression were reduced in UPA-treated leiomyoma, which is consistent with the rapid reduction in leiomyoma volume seen in the CDB and PEARL clinical trials.

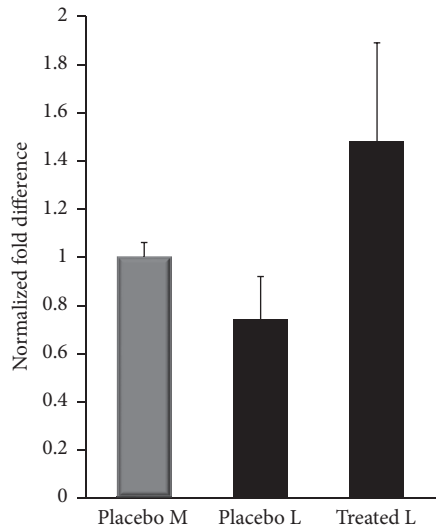

Figure 1: Fibrillin mRNA transcripts in placebo and ulipristal acetate treated patient samples.

Taken together, the clinical and laboratory data on ulipristal acetate suggests it may act via the rapid induction/alteration of osmoregulatory genes to change osmotic forces leading to an initial rapid reduction in leiomyoma volume over the first 3 months of treatment followed by a slower reduction in leiomyoma volume [92]. Work recently presented by Donnez and Dolmans reports that leiomyoma can be completely resolved with repeated doses of UPA, suggesting this medication may have more than one mechanism by which it acts to reduce leiomyoma. Evaluation of uterine leiomyoma treated longer than 3 months may be required to fully elucidate the mechanisms by which this medication exerts its effects.

7. Conclusions

Management of symptomatic uterine leiomyomata must be individually tailored to patient symptoms, desires for future fertility, age, and location of the leiomyoma. A list of the medications reviewed herein is included within Table 1.

The GnRH agonist, leuprolide acetate, had been considered to be superior to any other medication for reduction of symptoms and tumor burden. However, the side effect profile (vasomotor symptoms, vaginal dryness, potential cognitive impairment, bone loss associated with long-term use, and rebound of uterine volume with discontinuation) limits the usefulness of this class of medications. To circumvent several of the side effects of GnRH analogs, practitioners have employed hormone add-back therapy with good success.

The use of combined oral contraceptive pills and progesterone only formulations has demonstrated benefit in treating abnormal uterine bleeding and dysmenorrhea without definitive proof of either reduction or enhancement of uterine leiomyoma volume. Well-designed, randomized control trials should be performed to better elucidate the utility of hormonal medications in the long-term management of uterine leiomyoma.

Table 1: Medical management of symptomatic uterine fibroids.

	Dosing	Tx reduces leiomyoma volume?	Used to treat leiomyoma in the US?
	Nonsteroidal anti-inflammatory drugs (NSAIDs)		
Ibuprofen	600 mg orally daily starting on the first day of menstruation	No	Yes
Mefenamic acid	500 mg orally three times per day starting on the first day of menstruation	No	Yes
Naproxen	500 mg by mouth twice daily starting on the first day of menstruation	No	Yes
	Antifibrinolytics		
Tranexamic acid	1.3 g orally three times per day for 5 days	No	Yes
	10 mg/kg iv (maximum 600 mg/dose) every 8 hours	No	Yes
	Combined contraceptives		
Oral, transdermal Cyclic or noncyclic		No	Yes
	Progestin-only therapies		
Norethindrone-contraceptive pills	0.35 mg by mouth daily	No	Yes
Levonorgestrel releasing intrauterine device (IUD)	Intrauterine placement by healthcare professional; lasts 3–5 years depending on the device	No	Yes
Medroxyprogesterone (MPA)	Depo 150 mg intramuscularly every 12 weeks 2.5–10 mg orally 12–14 days/month	No	Yes
	Aromatase inhibitors		
Letrozole	2.5 mg orally for 12 weeks	Insufficient evidence	No
	Gonadotropin-releasing hormone (GnRH) analogs		
GnRH agonists			
Leuprolide acetate	Depot 7.5 mg intramuscularly every month Depot 22.5 mg intramuscularly every 3 months Depot 30 mg IM every 4 months Depot 45 mg IM every 6 months	Yes (30–65%), reversible	Yes
	Eligard: 7.5 mg subcutaneously (sq) monthly/22.5 mg sq every 3 months/30 mg every 4 months/45 mg sq every 6 months		No
	Leuprolide acetate: 1 mg sq daily		No
GnRH antagonists			
Cetrorelix	3 mg sq every 4 days Depot 60 mg sq on cycle day 2	Yes, reversible	No
	Antiprogestins		
Mifepristone	5–50 mg orally daily for 3–12 months	Insufficient evidence	No
	Selective Progesterone Receptor Modulators:		
Ulipristal acetate	10–20 mg po daily for 3 months	Yes (12–53%), appears to be a stable reduction	No*

* Approved for the presurgical treatment of symptomatic uterine leiomyoma in the European Union.

Given the prevalence, and morbidity, associated with uterine leiomyoma the promise of a long-term medical solution is encouraging with the advent of selective progesterone receptor modulators, most notably ulipristal acetate. This medication has been approved by the European regulatory agencies for use as a preoperative agent in women with symptomatic leiomyomata and anemia. Further work using this agent has shown complete resolution of uterine leiomyomata with repeated courses. There had been concern for endometrial pathology given the mechanism of action of the drug, but to this end the risk of development of endometrial hyperplasia or Type I endometrial carcinoma appears to be

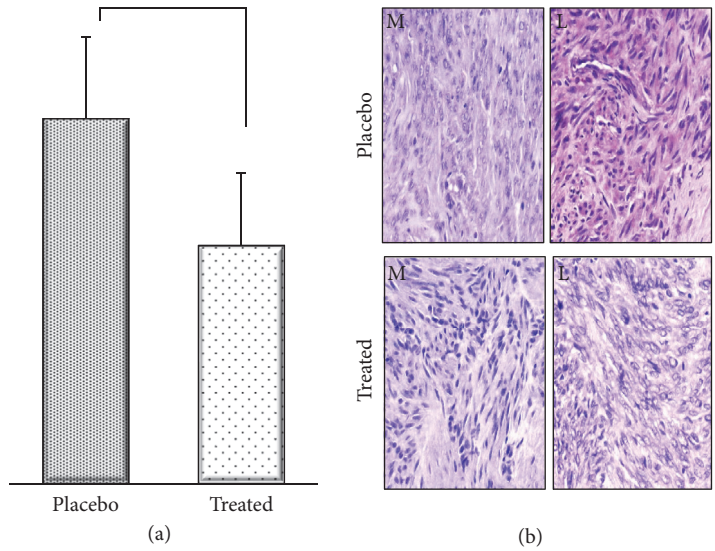

Figure 2: (a) Immunohistochemistry evaluation of TGF-β3 expression in patient matched myometrium (M) and leiomyoma (L) representative specimen. (b) Quantitation of TGF-β3 immunostaining revealing a decrease in TGF-β3 expression in treated leiomyoma, as compared to placebo.

very low. That being said, it is currently still advisable that treatment with this agent be followed closely for evidence of endometrial pathology.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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