REVIEW

# LEIOMYOMA AS AN INFERTILITY FACTOR: A SURGICAL REVIEW

**Francesca Frîncu[1,2], Antoine Edu[1,2], Mihai Cristian Dumitrașcu[1], Aida Petca[1], Andreea Velișcu[1], Claudia Mehedințu[1,2]**

[1]Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, [2]"Nicolae Malaxa" Clinical Hospital, Bucharest, Romania

Corresponding author: Antoine Edu
E-mail: antoine.edu@umfcd.ro

## Abstract

*Uterine fibroids are among the most common benign tumors in women of reproductive age. Their incidence is higher for African American women compared to Caucasian women. Women with fibroids may present with heterogeneous symptoms or may be diagnosed incidentally at routine checkups. Nowadays, a whole arsenal of diagnostic tools exists. Transvaginal ultrasound with color Doppler and 3D reconstruction, as well as hysteroscopy and nuclear magnetic resonance imaging (MRI), are the most useful. For the correct management of uterine fibroids, it is important to establish their location and type, according to existing classifications. Multiple studies have demonstrated their impact on fertility, especially in the case of submucosal, intracavitary ones. Most of the results in the literature on this issue come from assisted human reproduction clinics. This review aims to document the mechanisms by which uterine fibroids lead to low conception rates and clinical pregnancy rates and the available methods for their treatment to achieve pregnancy.*

**Keywords***: leiomyoma, infertility, minimally invasive, hysteroscopy, laparoscopy*

## Introduction

Uterine fibroids are the most common benign tumors in women of childbearing age [1], [2]. They consist of smooth muscle cells with a prominent extracellular matrix (ECM) and present heterogeneity in size, location, composition, and number [3]. Afro-American women have a higher incidence for leiomyoma, of almost 80% [4], [5], [6], with more severe clinical symptomatology compared to white women, who have an approximate incidence of 70% by their late 40's [7]. Some of the risk factors for uterine fibroids are nulliparity, early menarche, personal history of myoma, positive family history, increased BMI, increasing age during the reproductive time frame, and black race [2], [8], [9]. Fortunately, a balanced diet and a healthy way of life, as well as multiparity, proved to be protective factors [2]. Fibroids can be the cause of a multitude of symptoms or can be incidentally discovered on routine checkups. The most common clinical presentations are urinary and sexual dysfunctions, pressure or pain in the pelvic area, heavy menstrual bleeding, abnormal gynecological bleeding, and infertility [1], [10], [11]. At the ultrasound, fibroids are identified by the hypoechoic, well-circumscribed appearance, and circular flow with Doppler. 3D ultrasound mode or saline infusion helps determine localization (intracavitary, submucosal, intramural, subserosal), size, simultaneous presence in multiple locations, and whether the fibroid impinges into the uterine cavity [1], [12]. Precise determination helps

choose the right surgical approach: laparotomy, laparoscopy, or hysteroscopy.

The lack of randomized controlled studies (RCTs) between myomectomy and expectant management, with birth rates as endpoints, cannot determine a cause-effect relationship between fibroids and infertility. The state of knowledge comes from *in vitro* fertilization studies that use multiple variables in terms of infertility determination factors. 27% of patients who resort to assisted reproduction techniques (ART) present fibroids [13]. Moreover, infertility due to only fibroids appears in 1 to 3% of patients [14], [15].

To anticipate each type of fibroid's impact on a patient's reproduction ability, it is important to recognize each type and to set up the correct therapeutic management. This paper's aim is to emphasize the mechanisms by which uterine fibroids lead to infertility, as well as the current approaches to fibroid management in patients who wish to obtain a pregnancy.

## Materials and Method

Research of the literature was conducted in the databases of PubMed and EMBASE, to select full-length articles published in peer-reviewed journals up to 8th November 2021.

We used "MeSH" (PubMed) and "Emtree" (EMBASE) terms, but also free text words. We included cohort studies, reviews, systematic reviews, and meta-analyses. Conference abstract, letters, editorials and commentaries were excluded. The keywords included in the search strategy were leiomyoma/s, myoma, fertility, infertility, reproduction, surgery, hysteroscopy, laparoscopy, minimally invasive, laparotomy. Studies in other language than English were excluded.

## Results and Discussion

### *Pathophysiology and histopathology*

Monoclonal genetic alterations that arise in a single smooth muscle cell of the uterus trigger the development of myomas [16], [17]. The initiators of fibroids are still not well acknowledged, but estrogens (E) and progesterone (P), along with their receptors, are considered promoters of fibroid growth [18]. MicroRNAs are small non-protein-coding RNAs that target mRNAs for translational repression or cleavage [19]. Several miRNAs, such as miR-106b, miR-200, miR-93, let7, and miR-21, proved to be dysregulated and strongly associated with race and tumor size in uterine myomas compared to normal myometrium [20], [21], [22]. Some researchers found that mRNA and protein expression levels of estrogen receptor (ER) α and β are highly expressed in leiomyoma compared to normal myometrium [23]. It was demonstrated that E levels up the P receptors (PR) and P may promote myoma growth [24]. Moreover, E suppresses the normal p53 functions [25] and can alter the expression of multiple genes such as connexin 43 [26], insulin-like growth factor (IGF-1), IGFRs, MKP-1 [27], [28]. P downregulates the tumor necrosis factor (TNF α) [29] and IGF-1 expression [30] and upregulates the epidermal growth factor (EGF) [31], transforming growth factor (TGF) β3 [32], and B-cell lymphoma (Bcl) 2 protein [33] expression, thus contributes to leiomyoma cell growth and survival. In addition, epigenetic mechanisms, genetic alterations, and extracellular matrix components (ECM) highly contribute to the initiation and development of this kind of tumor [18].

Myomas are expanding tumors that grow between the normal smooth muscle cells. They surround themselves within a pseudocapsule, formed of fibro-neurovascular bundles. Macroscopic evaluation of adjacent myometrium and pseudocapsule shows a parallel arrangement of dense capillaries and large vessels forming the capsule with a separation from the myometrial vasculature by a narrow avascular cleft [34]. Ordinary leiomyomas are smooth muscle tumors that can degenerate or not. According to the degeneration, they can be classified into cystic, fatty, hemorrhagic, hyaline, or myxoid. Apart from the general of myomas, some intermediate variants can be either mitotically active, atypical, cellular, or smooth muscle tumors of uncertain malignant potential (STUMP) [35].

### *Diagnosis and classification*

Most classification systems evaluate uterine leiomyomas by their location. The size and

number are not currently included in the staging systems. Fibroids can be categorized as submucosal, intramural, and subserosal [36]. In 2011, Munro and colleagues subdivided leiomyomas and included them into the International Federation of Gynecology and Obstetrics (FIGO) classification of causes of abnormal uterine bleeding, as seen in Figure 1 [37]. Type 0 represents the pedunculated submucosal fibroid, whereas protrusion within the uterine cavity of more or less than 50% is represented by type I and type II, respectively. Type 3 fibroid intercepts the endometrium, while type 4 is entirely intramural, without contact with the serosa or the endometrium. Type 5 and type 6 are subserosal with their part in more than 50% intramural, and less than 50% respectively. Type 7 is pedunculated and subserosal, and type 8 is other (e.g. ligaments of the pelvis, cervix, fallopian tube, vagina) [38].

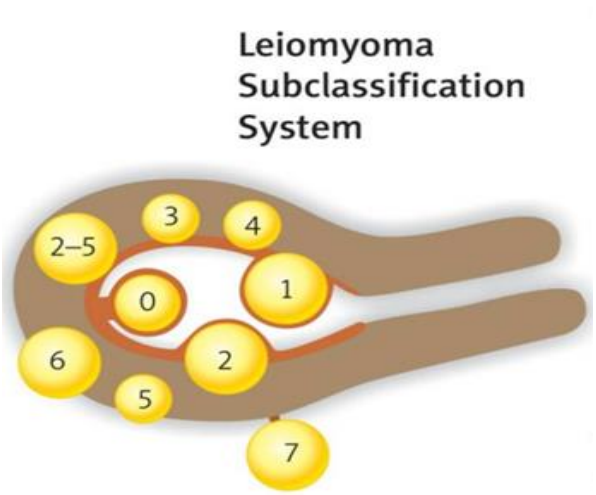


**Figure 1 – FIGO classification of fibroids [37]**

Any leiomyoma may undergo calcification, fibrosis, atrophy, or several degrees of degeneration [39].

As diagnostic methods, hysterosalpingography (HSG) and transvaginal ultrasound (TVUS) are the most used to assess the impact of fibroids on the uterine cavity. For the detection of intrauterine pathology, HSG has become an outdated method, as it has low sensitivity (50%) and specificity (20%), with unlikely precise fibroid localization [40].

Transvaginal ultrasonography scans (TVUS) have become a gold standard in the diagnosis of leiomyomas since the 1980s. At the ultrasound examination, leiomyomas appear as well-defined, concentric, and hypoechoic tumors that produce variable acoustic shadows. The level of fibrous tissue and calcification determines different grades of echogenicity. Leiomyomas usually appear hyperechogenic or isoechogenic. If necrosis appears, anechogenic components or "internal sonolucent areas" appear within the leiomyoma [41], [42]. In cervix localization of the leiomyomas (5%), the uterine canal might get obstructed and determine fluid accumulation in the endometrial canal that is easily recognized during examination [43]. Calcifications appear as echogenic foci with shadowing [44]. Color Doppler ultrasonography (Figure 2) is useful in vascularity assessment, showing circumferential flow around the lesion (perifibroid plexus – "the ring of fire" sign), a not very well represented central flow, and the peripheral centripetal arterial branches that supply the leiomyoma [44], [45]. Moreover, torsional or necrotic fibroids will present low or absent blood flow [44], [46]. The differential diagnosis of leiomyomas is extremely important as it starts with the clinical presentation and continues with ultrasound examination. The most common pathologies to be misdiagnosed are endometrial polyps, adenomyosis, and solid tumors of the adnexa. Adenomyosis is difficult to be diagnosed ultrasonographically and can be misdiagnosed with intramural leiomyomas. Suggestive ultrasound features for adenomyosis are the vascular spaces and radial stripes that may provide a visual effect named "rain in the forest sign", thickened uterine wall, subendometrial echoic linear striations, heterogeneous echotexture, thickened junctional zone with unclear myometrial/endometrial margins [36], [47-49]. In contrast to leiomyomas that cause enlargement of the uterus with an altered outline, adenomyosis determines a globular, enlarged, with regular external outline uterus [50]. Intrauterine benign masses, such as submucosal fibroids and endometrial polyps, can be easily mistaken and may result in improper management and possible injury to the patient. The endometrial polyps appear as homogeneous hyperechogenic structures in the uterine cavity, whereas submucosal fibroids' echogenicity may vary from hypoechogenic, isoechogenic, to hyperechogenic or mixed, depending on the nature and size of the fibroid [51]. In the case of submucosal fibroids, the distance between the uterus surface and the outer margin of the fibroid

called the minimal free myometrial margin has to be measured. This is important for the decision of hysteroscopic removal when the minimal free margin is ranged between 5 and 10 mm [52]. Submucosal myomas represent approximately 5-10% of all leiomyomas and tend to be bothersome clinically, causing infertility due to distortion of the uterine cavity and menorrhagia. Also, when a pedunculated submucosal fibroid gets torsioned, the risk for infection and necrosis increase [49]. Doppler ultrasound helps in differentiating between the submucosal fibroids and adenomyosis, with diffusely spread vessels, from the endometrial polyp, with a single feeding vessel [50]. 3D TVUS (Figure 3) in association with saline instillation provides more information in differentiating submucosal leiomyomas from endometrial polyps [53]. In addition, when a submucous myoma undergoes cystic degeneration, a "honeycomb pattern" may appear, thus misleading the examiner for an endometrial pathology [54]. Malignant myometrial lesions, such as STUMP and leiomyosarcoma, should always be ruled out. Shortly, a large myometrial tumor, with irregular vascular distribution, high peak velocity, low impedance to flow, and inhomogeneous compact structure (absence of "radial stripy echogenicity", irregular anechoic areas due to necrosis), may suggest malignancy [49], [55].

Magnetic resonance imaging (MRI) is the most accurate evaluation for uterine fibroids. The indications for MRI are reserved for equivocal ultrasound findings, to establish the histological origin of the masses (i.e. differential diagnosis with malignant tumors and adenomyosis) and their anatomical origin (e.g. uterine vs. intestinal, adnexal, etc.) [56], [57]. MRI provides additional information in the diagnosis of leiomyomas, having a sensitivity of 86-92% and a specificity of 100% [58].

*Uterine leiomyomas and infertility*

About 1 to 3% of infertile women present leiomyomas as the only cause for infertility and 27% of women who address reproductive assistance present fibroids [59], [60]. Following FIGO classification, types 0-2 of fibroids are responsible for low pregnancy rates and decreased implantation [61].

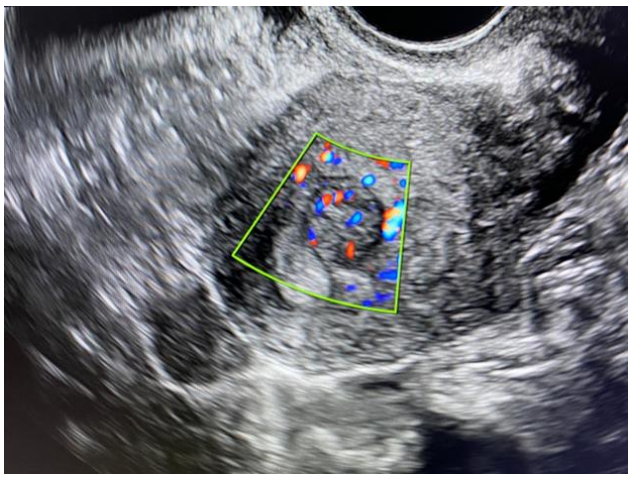

**Figure 2 – Transvaginal color Doppler view of type 3 (FIGO) leiomyoma (From Prof. Dr. Claudia Mehendinţu's collection)**

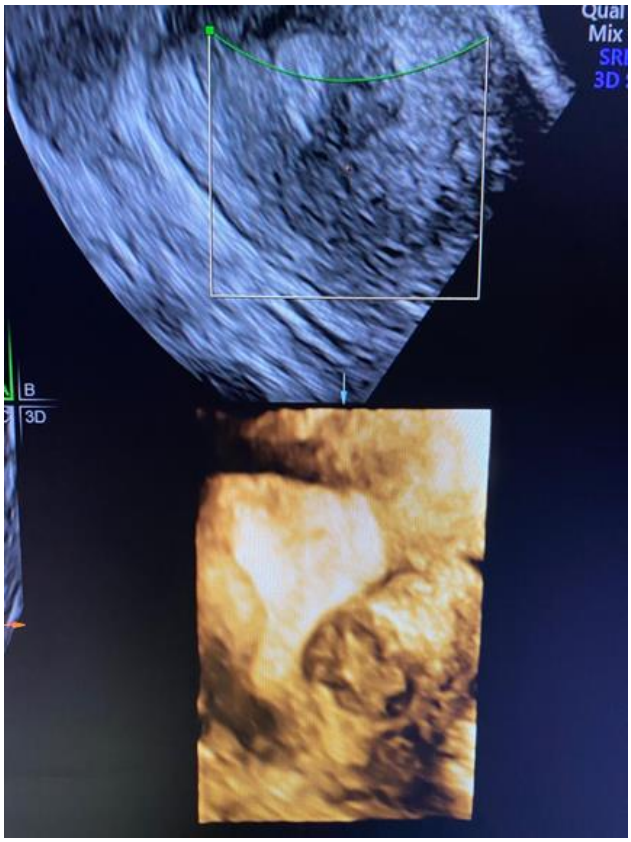


**Figure 3 – The same leiomyoma observed with 3D acquisition in the coronal plane; it is easy to see how the leiomyoma is completely intramural, but abuts the endometrium (From Prof. Dr. Claudia Mehendinţu's collection)**

Pritts et al. conducted a meta-analysis analyzing 23 studies on fibroids and their impact on fertility outcomes. Their results showed decreased rates at 72% for implantation (95%CI; RR:0.283; p=0.003) and 67% for ongoing pregnancies/live births (95%CI; RR:0.318; p<0.001). Moreover, the spontaneous abortion rate increases up to 68% in women that present

submucosal fibroids compared to those without fibroids; subserosal fibroids were considered negligible in the impact on reproductive outcomes [61].

The mechanisms that interfere with fertility outcomes in the presence of myomas may coexist. The size, number, and location are important variables that have to be under consideration. Anomalous endometrial contour caused by a distorted uterine cavity alters the sperm transport. An enlarged, deformed uterus may compromise sperm progression not only by cervical displacement but also through modified myometrial contractility. In addition, deviation or obstruction of the ostia may compromise tubal patency and tubo-ovarian relationship of ovum collection. Retained menstrual blood due to a deformity of the uterus and impeded endometrial and myometrial vascularization due to underlying fibromas may hinder sperm transport and implantation. Moreover, the chronic inflammatory reaction in the proximity of the myoma alters the endometrial milieu [62], [63], [64-68]. There are histological changes in the endometrium that overlies leiomyomas, such as atrophy, elongation, ulceration, cystic glandular hyperplasia, polyposis, distortion of the endometrial glands, endometrial venule ectasia [68-71]. Studies revealed that endometrial receptivity in a fibroid uterus expresses a global reduction in HOX gene expression, playing an important role in fertility impairment [68], [72].

Most of the current studies show that subserosal myomas don't generate a substantial effect on fertility potential, and their removal doesn't bring a considerable benefit [61], [62], [67], [73]. In contrast, intramural fibroids have gained increased attention, especially in the assisted reproduction field [74]. In line with this, Sunkara and colleagues focused on the cause-effect relationship between intramural myomas and fertility and found an association with decreased live birth rates [75]. In addition, intramural fibroids localization near the cervix or the tubal ostium may compromise sperm progression and fertilization [74].

*Leiomyoma treatment from the fertility point of view*

These days, there is a large variety of surgical and medical options for uterine myomas treatment. Minimal invasive techniques, such as hysteroscopy and laparoscopy, earned more interest in the last several years. Less invasive alternative methods, such as uterine artery embolization, and noninvasive techniques, such as high frequency magnetic resonance-guided focused ultrasound surgery (MRgFUS), have emerged as an alternative for patients who do not desire surgery [74].

Depending on the type and number of the fibroids, surgical intervention may be chosen. For submucosal myomas (Figure 4), the standard recommendation remains the hysteroscopically approach (Figure 5). This can either be performed with mechanical instruments (mechanical "cold" loops and scissors), electrocautery (vaporizing electrodes and thermal loops), intrauterine morcellation, or laser fibers ("touch" or Yag laser "no-touch" technique) [76], [77]. From the fertility aspect, for types 1 and 2 (according to FIGO classification), the "cold" loop myomectomies are preferred over "resectoscope slicing" which can damage the healthy myometrium. The so-called "cold" loop technique combines both mechanical blunt dissections, with enucleation of the intramural component and monopolar electrocautery for the intracavitary component [74].

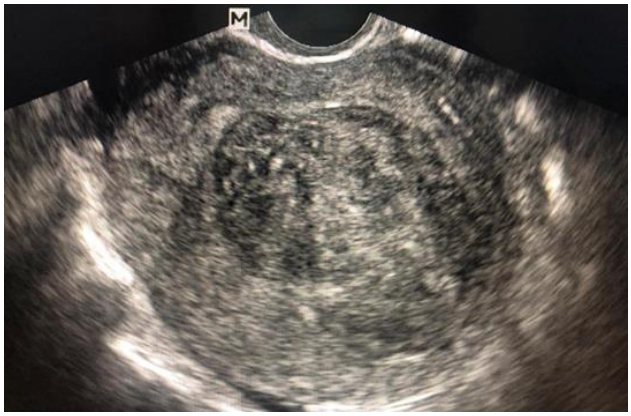

**Figure 4 – Ultrasonographic view of an intracavitary, submucosal leiomyoma (From Prof. Dr. Claudia Mehendinţu's collection)**

Pritts et al. showed that surgical removal of the submucosal fibroids increases (RR 1.72; 95% CI 1.13–2.58) pregnancy rates and restore live birth rates (RR 0.98; 95% CI 0.45–2.41) [73]. Similarly, Bulleti et al. demonstrated that women who undergo submucosal fibroids myomectomy have more chances for conceiving than those unoperated (42% vs 11%) [78].

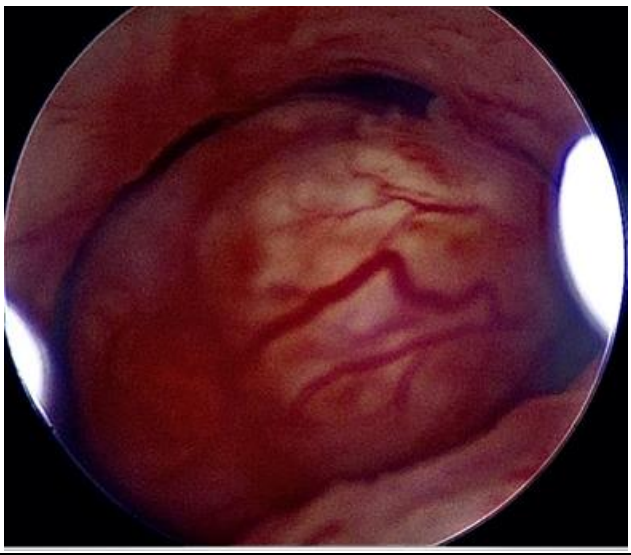

**Figure 5 – Hysteroscopic view of the same submucosal leiomyoma as in Figure 4**

Additionally, Casini et al. showed that pregnancy rates are higher in women who chose the surgical treatment of the submucosal fibroids than those who opt for expectant management (43% vs. 27%) [79]. For the large submucosal myomas, GnRH-agonists' administration before hysteroscopic resection would be useful. This medication decreases endometrial thickness, the fibroid's volume, blood flow, and minimizes the fluid overload during the hysteroscopic procedure [80]. Makris et al. showed a pregnancy rate of 54% after hysteroscopic myomectomy with fibroids being the only cause of infertility [81]. Comparably, Shokeir et al. showed a drop in the miscarriage rate from 61,6 to 26,3% and an increased pregnancy rate, from 3,8% to 63,2%, in women who adopted surgical treatment for the submucosal fibroids [82]. In a study with 41 infertile women, 60,9% obtained a pregnancy after hysteroscopic myomectomy [83]. Hysteroscopic myomectomy can lead to intrauterine adhesions that can interfere with conception, even though it is considered a procedure with minimal adverse effects [84], [85].

If the fibroids are larger than 4 to 6 cm, or if there are multiple fibroids, laparotomy or laparoscopy may be taken into consideration for myomectomies. However, myomas present high recurrence and hysterectomy represents the definitive treatment in women that are not interested in preserving fertility [68]. In 2012, Beneck et al. affirmed that intramural fibroids impact the pregnancy outcomes at the in vitro fertilization (IVF)/ intracytoplasmic sperm injection (ICSI) cycles and myomectomy should be performed. Women with intramural fibroids presented an implantation rate of 27,7% compared to the control group with 16,4% [67]. Casini et al. also showed significantly improved rates of pregnancy in women with a combination of submucosal and intramural fibroids (36% vs. 15%) [79]. Bulleti et al. compared women with intramural and large subserosal fibroids who underwent myomectomy before IVF treatment with those who chose expectant/conservative management. The pregnancy rate increased from 15% to 34% in the myomectomy group [78]. A laparoscopic technique, called myolysis, involves the insertion of cryoprobes, fiberoptic lasers, electrocautery needles, with subsequent thermal destruction of the fibroids [86]. Laparoscopic procedures appear to be in favor of abdominal myomectomies (Figure 6), (Figure 7), (Figure8), with a reduced risk for consequent uterine rupture, reduced operating time, blood loss, shorter hospital stay, and increased recovery time. In the laparoscopic approach (Figure 9), (Figure 10), (Figure 11), (Figure 12), (Figure 13), removal of the fibroid specimens from the peritoneal cavity may be performed either by a mini-laparotomy or by morcellation (Figure 14). Most studies did not find significant differences between laparoscopic and abdominal myomectomies, in terms of pregnancy rates and live-birth rates [65], [87], [88].

**Figure 6 – Abdominal myomectomy: enucleation of a type 4 (FIGO) leiomyoma (From Prof. Dr. Claudia Mehendințu's collection)**

It is important not to forget that myomectomies are associated with adhesion formation, especially in the posterior compartment of the uterus. Also, intrauterine synechiae may appear after hysteroscopic management of leiomyomas [89]. An early second-look hysteroscopy should be performed between one to three weeks after myomectomy, to identify mild or moderate adhesions and to prevent them [90].

**Figure 7 – Abdominal myomectomy: the sutured uterus following myomectomy (From Prof. Dr. Claudia Mehendinţu's collection)**

**Figure 8 – Specimen of leiomyoma after abdominal myomectomy (From Prof. Dr. Claudia Mehendinţu's collection)**

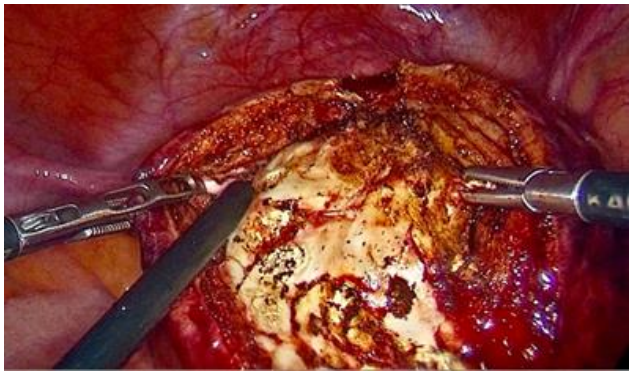

**Figure 9 – Laparoscopically enucleation of a type 5 (FIGO) leiomyoma (From Prof. Dr. Claudia Mehendinţu's collection)**

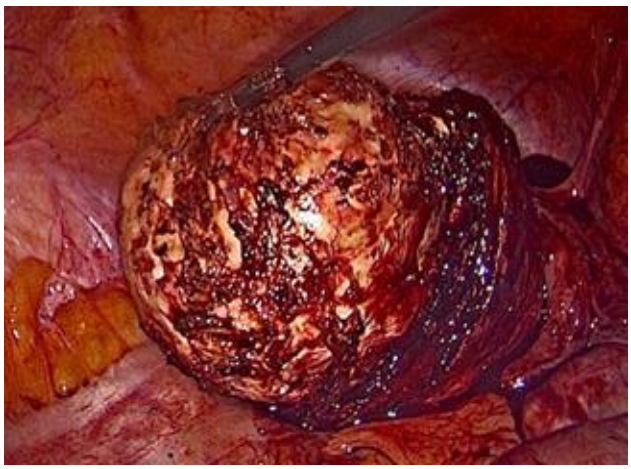

**Figure 10 – Laparoscopically enucleation of a type 5 (FIGO) leiomyoma (From Prof. Dr. Claudia Mehendinţu's collection)**

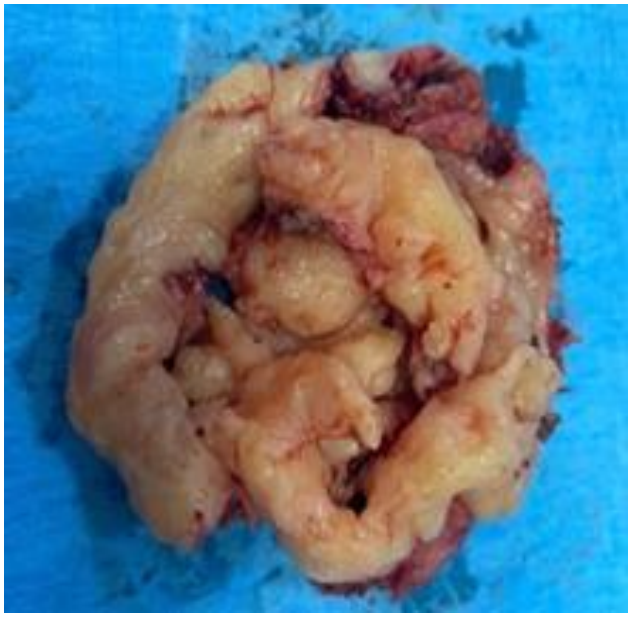

**Figure 11 – Specimens of leiomyoma after laparoscopic morcellation (From Prof. Dr. Claudia Mehendinţu's collection)**

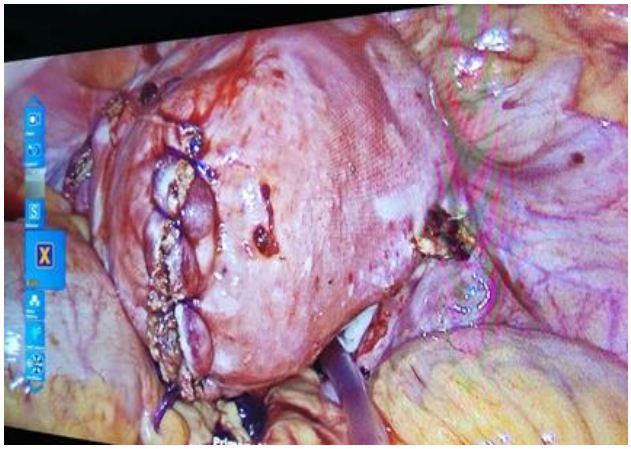

**Figure 12 – Laparoscopically sutured uterus (From Prof. Dr. Claudia Mehendinţu's collection)**

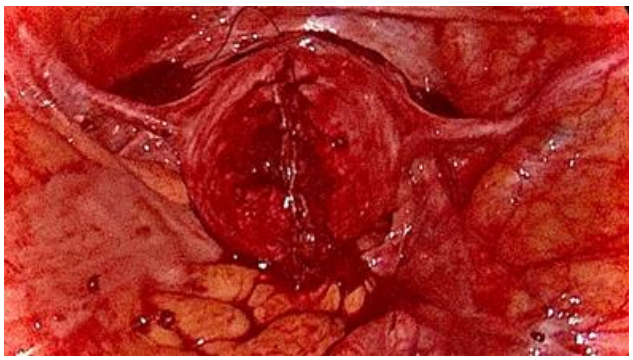

**Figure 13 – Laparoscopically sutured uterus (From Prof. Dr. Claudia Mehendinţu's collection)**

**Figure 14 – Specimens of leiomyoma after hysteroscopic morcellation (From Prof. Dr. Claudia Mehendinţu's collection)**

## Conclusion

Leiomyomas are one of the most common benign uterine tumors and present a remarkable prevalence among women with a considerable impact on reproductive life.

Submucosal leiomyomas have been undoubtedly linked to reduced fertility. The evidence is not so abundant for the intramural fibroids therefore research and more randomized controlled studies are needed. Myomectomy definitely improves fertility in patients with submucosal myomas and should be the treatment of choice in women with a desire for conception.

## References

[1] Wise LA, Laughlin-Tommaso SK. Epidemiology of uterine fibroids: from menarche to menopause. Clin Obstet Gynecol 2016;59(01): 2–24

[2] Sparic R, Mirkovic L, Malvasi A, Tinelli A. Epidemiology of uterine myomas: a review. Int J Fertil Steril 2016;9(04):424–435

[3] Marsh EE, Steinberg ML, Parker JB, Wu J, Chakravarti D, Bulun SE. Decreased expression of microRNA-29 family in leiomyoma contributes to increased major fibrillar collagen production. Fertil Steril 2016;106(03):766–772

[4] Day Baird D, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative inci- dence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003;1:100–107

[5] Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, Willett WC, Hunter DJ. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol 1997;6:967–973.

[6] Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003;188 (01):100–107

[7] Kjerulff KH, Langenberg P, Seidman JD, Stolley PD, Guzinski GM. Uterine leiomyo- mas. Racial differences in severity, symptoms and age at diagnosis. J Reprod Med 1996;7:483–490.

[8] Luoto R, Kaprio J, Rutanen EM, Taipale P, Perola M, Koskenvuo M. Heritability and risk factors of uterine fibroids–the Finnish Twin Cohort study. Maturitas 2000;37(01):15–26

[9] Sato F, Mori M, Nishi M, Kudo R, Miyake H. Familial aggregation of uterine myomas in Japanese women. J Epidemiol 2002;12 (03):249–253

[10] Fleischer R, Weston GC, Vollenhoven BJ, Rogers PA. Pathophy- siology of fibroid disease: angiogenesis and regulation of smooth muscle proliferation. Best Pract Res Clin Obstet Gynaecol 2008; 22(04):603–614

[11] Dagur G, Suh Y, Warren K, Singh N, Fitzgerald J, Khan SA. Urological complications of uterine leiomyoma: a review of literature. Int Urol Nephrol 2016;48(06):941–948

[12] Groszmann YS, Benacerraf BR. Complete evaluation of anatomy and morphology of the infertile patient in a single visit; the modern infertility pelvic ultrasound examination. Fertil Steril 2016;105(06):1381–1393

[13] BullettiC, DEZieglerD, LeviSettiP, CicinelliE, PolliV, Stefanetti M. Myomas, pregnancy outcome, and in vitro fertilization. Ann NY Acad Sci 2004;1034:84–92

[14]Zepiridis LI, Grimbizis GF, Tarlatzis BC. Infertility and uterine fibroids. Best Pract Res Clin Obstet Gynaecol 2016;34:66–73
[15] Rackow BW, Arici A. Fibroids and in-vitro fertilization: which comes first? Curr Opin Obstet Gynecol 2005;17(03):225–231
[16] Kim J. J., Sefton E. C. The role of progesterone signaling in the pathogenesis of uterine leiomyoma. Molecular and Cellular Endocrinology. 2012;358(2):223–231. doi: 10.1016/j.mce.2011.05.044.
[17] Rein MS, Friedman AJ, Barbieri RL, Pavelka K, Fletcher JA, Morton CC. Cytogenic abnormalities in uterine leiomyomata. Obstet Gynecol 1991;77:923–6.
[18] Islam MS, Protic O, Stortoni P, Grechi G, Lamanna P, Petraglia F, Castellucci M, Ciarmela P Fertil Steril. 2013 Jul; 100(1):178-93
[19] Miska EA. How microRNAs control cell division, differentiation and death. Curr Opin Genet Dev 2005;15:563–8.
[20] Marsh EE, Lin Z, Yin P, Milad M, Chakravarti D, Bulun SE. Differential ex- pression of microRNA species in human uterine leiomyoma versus normal myometrium. Fertil Steril 2008;89:1771–6.
[21] Pan Q, Luo X, Chegini N. Differential expression of microRNAs in myome- trium and leiomyomas and regulation by ovarian steroids. J Cell Mol Med 2008;12:227–40.
[22] Georgieva B, Milev I, Minkov I, Dimitrova I, Bradford AP, Baev V. Character- ization of the uterine leiomyoma microRNAome by deepsequencing. Ge- nomics 2012;93:275–81.
[23] Ishikawa H, Reierstad S, Demura M, Rademaker AW, Kasai T, Inoue M, et al. High aromatase expression in uterine leiomyoma tissues of African-American women. J Clin Endocrinol Metab 2009;94:1752–6.
[24] Ishikawa H, Ishi K, Serna VA, Kakazu R, Bulun SE, Kurita T. Progesterone is essential for maintenance and growth of uterine leiomyoma. Endocrinol- ogy 2010;151:2433–42.
[25] Gao Z, Matsuo H, Nakago S, Kurachi O, Maruo T. p53 Tumor suppressor protein content in human uterine leiomyomas and its down-regulation by 17 beta-estradiol. J Clin Endocrinol Metab 2002;87:3915–20.
[26] Andersen J, Grine E, Eng CL, Zhao K, Barbieri RL, Chumas JC, et al. Expres- sion of connexin-43 in human myometrium and leiomyoma. Am J Obstet Gynecol 1993;169:1266–76.
[27] Lee EJ, Bajracharya P, Lee DM, Cho KH, Kim KJ, Bae YK, et al. Gene expres- sion profiles of uterine normal myometrium and leiomyoma andtheir es- trogen responsiveness in vitro. Korean J Pathol 2010;44:272–83.
[28] Swartz CD, Afshari CA, Yu L, Hall KE, Dixon D. Estrogen-induced changes in IGF-I, Myb family and MAP kinase pathway genes in human uterine leio- myoma and normal uterine smooth muscle cell lines. Mol Hum Reprod 2005;11:441–50.
[29] Kurachi O, Matsuo H, Samoto T, Maruo T. Tumor necrosis factor-a expres- sion in human uterine leiomyoma and its down-regulation by progester- one. J Clin Endocrinol Metab 2001;86:2275–80.
[30] Yamada T, Nakago S, Kurachi O, Wang J, Takekida S, Matsuo H, et al. Pro- gesterone down-regulates insulin-like growth factor-I expression in cul- tured human uterine leiomyoma cells. Hum Reprod 2004;19:815–21.
[31] Shimomura Y, Matsuo H, Samoto T, Maruo T. Up-regulation by progester- one of proliferating cell nuclear antigen and epidermal growth factor ex-pression in human uterine leiomyoma. J Clin Endocrinol Metab 1998;83: 2192–8.
[32] Arici A, Sozen I. Transforming growth factor-beta3 is expressed at high levels in leiomyoma where it stimulates fibronectin expression and cell pro-liferation. Fertil Steril 2000;73:1006–11.
[33] Matsuo H, Maruo T, Samoto T. Increased expression of Bcl-2 protein in hu- man uterine leiomyoma and its up-regulation by progesterone. J Clin Endo- crinol Metab 1997;82:293–9.
[34] Tinelli A, Malvasi A, Rahimi S, Negro R, Cavallotti C, Vergara D, Vittori G, Mettler L. Myoma pseudocapsule: a distinct endocrino-anatomical entity in gynecological surgery. Gynecol Endocrinol. 2009 Oct;25(10):661-7. doi: 10.1080/09513590903015502. PMID: 19526398.
[35] Arleo EK, Schwartz PE, Hui P, et al. Review of leiomyoma vari- ants. AJR. 2015;205:912–21.
[36] McLucas B. Diagnosis, imaging and anatomical classification of uterine fibroids. Best Pract Res Clin Obstet Gynaecol. 2008;22:627–642
[37] Munro MG, Crithcley HOD, Fraser IS, for the FIGO Working Group on Menstrual Disorders. The FIGO classification of causes of abnormal uterine bleeding. Int J Gynaecol Obstet. 2011; 113(1):1–2.
[38] Kinkel K, Ascher SM, Reinhold C. Benign Disease of the Uterus. 2018 Mar 21. In: Hodler J, Kubik-Huch RA, von Schulthess GK, editors. Diseases of the Abdomen and Pelvis 2018-2021: Diagnostic Imaging - IDKD Book [Internet]. Cham (CH): Springer; 2018. Chapter 3. PMID: 31314373.
[39] Parker WH. Etiology, symptomatology, and diagnosis of uterine myomas. Fertil Steril. 2007 Apr;87(4):725-36. doi: 10.1016/j.fertnstert.2007.01.093. PMID: 17430732.
[40] Soares SR, Barbosa dos Reis MM, Camargos AF. Diagnostic accuracy of sonohysterography, transvaginal sonography, and hysterosalpingography

in patients with uterine cavity diseases. Fertil Steril. 2000;73:406–411
[41] Rashid SQ, Chou YH, Tiu CM, et al. Ultrasonography of uterine leiomyomas. J Med Ultrasound. 2016;24:3e12
[42] Valentin L. Characterizing acute gynaecological pathology with ultrasound: an overview and case examples. Best Pract Res Clin Obstet Gynaecol. 2009 Oct; 23(5):577-93
[43] Wallach EE, Vlahos NF. Uterine myomas: an overview of development, clinical features, and management. Obstet Gynecol. 2004 Aug; 104(2):393-406
[44] Wilde S, Scott-Barrett S. Radiological appearances of uterine fibroids. Indian J Radiol Imaging. 2009;19(3):222-231. doi:10.4103/0971-3026.54887
[45] Amant F, Coosemans A, Debiec-Rychter M, et al. Clinical management of uterine sarcomas. Lancet Oncol. 2009;10:1188.
[46] Van den Bosch T, Van Schoubroeck D. Ultrasound diagnosis of endometriosis and adenomyosis: State of the art. Best Pract Res Clin Obstet Gynaecol. 2018 Aug;51:16-24. doi: 10.1016/j.bpobgyn.2018.01.013. Epub 2018 Feb 14. PMID: 29506961.
[47] Sakhel K, Abuhamad A. Sonography of adenomyosis. J Ultrasound Med. 2012 May;31(5):805-8. doi: 10.7863/jum.2012.31.5.805. PMID: 22535729.
[48] Exacoustos C, Brienza L, Di Giovanni A, et al. Adenomyosis: three-dimensional sonographic findings of the junctional zone and correlation with histology. Ultrasound Obstet Gynecol. 2011 Apr; 37(4):471-9
[49] Testa AC, Di Legge A, Bonatti M, Manfredi R, Scambia G. Imaging techniques for evaluation of uterine myomas. Best Pract Res Clin Obstet Gynaecol. 2016 Jul;34:37-53. doi: 10.1016/j.bpobgyn.2015.11.014. Epub 2015 Nov 30. PMID: 26803557.
[50] Exacoustos C, Romanini ME, Amadio A, et al. Can gray-scale and color Doppler sonography differentiate between uterine leiomyosarcoma and leiomyoma? J Clin Ultrasound. 2007 Oct; 35(8):449-57
[51] Woźniak A, Woźniak S. Ultrasonography of uterine leiomyomas. Prz Menopauzalny. 2017;16(4):113-117. doi:10.5114/pm.2017.72754
[52] Ludwin A, Ludwin I, Pityński K, et al. Transrectal ultrasound-guided hysteroscopic myomectomy of submucosal myomas with a varying degree of myometrial penetration. J Minim Invasive Gynecol. 2013 Sep-Oct; 20(5):672-85
[53] Czuczwar P, Wozniak S, Szkodziak P, et al. Elastography improves the diagnostic accuracy of sonography in differentiating endometrial polyps and submucosal fibroids. J Ultrasound Med. 2016;35:2389–2395.
[54] Cohen JR, Luxman D, Sagi J, et al. Ultrasonic "honeycomb" appearance of uterine submucous fibroids undergoing cystic degeneration. J Clin Ultrasound. 1995 Jun; 23(5):293- 6
[55] Minsart AF, Ntoutoume Sima F, Vandenhoute K, Jani J, Van Pachterbeke C. Does three-dimensional power Doppler ultrasound predict histopathological findings of uterine fibroids? A preliminary study. Ultrasound Obstet Gynecol. 2012 Dec;40(6):714-20. doi: 10.1002/uog.11155. Epub 2012 Nov 16. PMID: 22581621.
[56] Bonneau C, Thomassin-Naggara I, Dechoux S, et al. Value of ultrasonography and magnetic resonance imaging for the characterization of uterine mesenchymal tumors. Acta Obstet Gynecol Scand. 2014 Mar;93(3):261-8
[57] Yang Q, Zhang LH, Su J, Liu J (2011) The utility of diffusion-weighted MR imaging in differentiation of uterine adenomyosis and leiomyoma. European journal of radiology. 2011: 79:e47-51.
[58] Jondal DE, Wang J, Chen J, et al. Uterine fibroids: correlation between MRI appearance and stiffness via magnetic resonance elastography. Abdom Radiol (NY) 2017 doi: 10.1007/s00261-017-1314-1.
[59] BullettiC, DEZieglerD, LeviSettiP, CicinelliE, PolliV, Stefanetti M. Myomas, pregnancy outcome, and in vitro fertilization. Ann NY Acad Sci 2004;1034:84–92
[60] Zepiridis LI, Grimbizis GF, Tarlatzis BC. Infertility and uterine fibroids. Best Pract Res Clin Obstet Gynaecol 2016;34:66–73
[61] Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009; 91(04):1215–1223
[62] Somigliana E, Vercellini P, Daguati R, Pasin R, De Giorgi O, Crosignani PG. Fibroids and female reproduction: a critical analysis of the evidence. Hum Reprod Update. 2007;13:465–476.
[63] Buttram VC, Jr, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril. 1981;36:433–445.
[64] Horne AW, Critchley HO. The effect of uterine fibroids on embryo implantation. Semin Reprod Med. 2007;25:483–489.
[65] Practice Committee of American Society for Reproductive Medicine in collaboration with Society of Reproductive Surgeons. Myomas and reproductive function. Fertility and Sterility. 2008;90(5):S125–S130. doi: 10.1016/j.fertnstert.2008.09.012.
[66] Donnez J., Jadoul P. What are the implications of myomas on fertility? A need for a debate? Human Reproduction. 2002;17(6):1424–1430. doi: 10.1093/humrep/17.6.1424.

[67] Benecke C., Kruger T. F., Siebert T. I., Van der Merwe J. P., Steyn D. W. Effect of fibroids on fertility in patients undergoing assisted reproduction. A structured literature review. 2005;59:225–30.
[68] Cook H, Ezzati M, Segars JH, McCarthy K. The impact of uterine leiomyomas on reproductive outcomes. Minerva Ginecol. 2010;62(3):225-236.
[69]Deligdish L., Loewenthal M. Endometrial changes associated with myomata of the uterus. Journal of Clinical Pathology. 1970;23(8):676–680. doi: 10.1136/jcp.23.8.676.
[70] Maguire M, Segars JH. Benign uterine disease: leiomyomata and benign polyps. In: Aplin JD, Fazleabas AT, Glasser SR, Giudice LC, editors. The Endometrium: Molecular, Cellular and Clinical Perspectives. 2nd Edition. Informa HealthCare; London, UK: 2008. pp. 797–812.
[71] Sharma SP, Misra SD, Mittal VP. Endometrial changes--a criterion for the diagnosis of submucous uterine leiomyoma. Indian J Pathol Microbiol. 1979 Jan;22(1):33-6. PMID: 544482.
[72] Rackow B. W., Taylor H. S. Submucosal uterine leiomyomas have a global effect on molecular determinants of endometrial receptivity. Fertility and Sterility. 2010;93(6):2027–2034. doi: 10.1016/j.fertnstert.2008.03.029.
[73] Pritts E. A. Fibroids and infertility: a systematic review of the evidence. Obstetrical and Gynecological Survey. 2001;56(8):483–491. doi: 10.1097/00006254-200108000-00022.
[74] Vlahos NF, Theodoridis TD, Partsinevelos GA. Myomas and Adenomyosis: Impact on Reproductive Outcome. Biomed Res Int. 2017;2017:5926470. doi:10.1155/2017/5926470
[75] Sunkara S. K., Khairy M., El-Toukhy T., Khalaf Y., Coomarasamy A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Human Reproduction. 2010;25(2):418–429. doi: 10.1093/humrep/dep396
[76] Di Spiezio Sardo A., Mazzon I., Bramante S., et al. Hysteroscopic myomectomy: a comprehensive review of surgical techniques. Human Reproduction Update. 2008;14(2):101–119. doi: 10.1093/humupd/dmm041.
[77] Loffer F. D. Hysteroscopic endometrial ablation with the ndiyag laser using a nontouch technique. Obstetrics and Gynecology. 1987;69(4):679–682.
[78] Bulletti C, De Ziegler D, Setti PL, Cicinelli E, Polli V, Stefanetti M. Myomas, pregnancy outcome, and in vitro fertilization. Ann N Y Acad Sci. 2004;1034:84–92.
[79] Casini ML, Rossi F, Agostini R, Unfer V. Effect of the position of fibroids on fertility. Gynecol Endocrinol. 2006;22:106–109.
[80] Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update. 2016;22(6):665-686. doi:10.1093/humupd/dmw023
[81] Makris N, Vomvolaki E, Mantzaris G, Kalmantis K, Hatzipappas J, Antsaklis A. Role of a bipolar resectoscope in subfertile women with submucous myomas and menstrual disorders. J Obstet Gynaecol Res 2007;33(06):849–854
[82] Shokeir TA. Hysteroscopic management in submucous fibroids to improve fertility. Arch Gynecol Obstet 2005;273(01):50–54
[83] Giatras K, Berkeley AS, Noyes N, Licciardi F, Lolis D, Grifo JA. Fertility after hysteroscopic resection of submucous myomas. J Am Assoc Gynecol Laparosc 1999;6(02):155–158
[84] Jefferys A, Akande V. Modern management of fibroids. Obstet Gynaecol Reprod Med 2016;26(05):127–132
[85] Whynott RM, Vaught KCC, Segars JH. The Effect of Uterine Fibroids on Infertility: A Systematic Review. Semin Reprod Med. 2017 Nov;35(6):523-532. doi: 10.1055/s-0037-1607295. Epub 2017 Nov 3. PMID: 29100240.
[86] Zupi E, Sbracia M, Marconi D, Munro MG. Myolysis of uterine fibroids: is there a role? Clin Obstet Gynecol 2006;49:821–33.
[87] Seracchioli R, Rossi S, Govoni F, Rossi E, Venturoli S, Bulletti C, et al. Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy. Hum Reprod 2000;15:2663–8.
[88] Vercellini P, Bocciolone L, Colombo A, Vendola N, Meschia M, Bolis G. Gonadotropin releasing hormone agonist treatment before hysterectomy for menorrhagia and uterine leiomyomas. Acta Obstet Gynecol Scand 1993;72:369–73.
[89] Mazzon I. Palermo, Italy: COFESE: 1995. Nuova technical per la miometomia isteroscopia: enucleazione con ansa fredda.
[90] Di Spiezio Sardo A., Calagna G., Scognamiglio M., O'Donovan P., Campo R., De Wilde R. L. Prevention of intrauterine post-surgical adhesions in hysteroscopy. A systematic review. European Journal of Obstetrics Gynecology and Reproductive Biology. 2016; 203:182–192.