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Guidelines for diagnosis and treatment of fibromyomatosis

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INTRODUCTION

AUTHORS: These Recommendations have been written by a group of medical professionals (Drafters) identified by SIGO, AOGOI and AGUI Scientific Committees with the organisational support of the Confalonieri-Ragonese Foundation.

RECIPIENTS: These Recommendations are addressed to all professionals who deal with the diagnosis and treatment of the diseases covered by these guidelines.

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METHODS

Writing medical Recommendations is a complex activity in terms of methods, and requires advanced technical skills, resources and time that companies usually are not able to provide. These recommendations are based on systematic reviews. Today, however, acquiring the critical skills required to assess the extent to which systematic reviews (or already existing Guidelines/recommendations produced in Italy or in other countries) are sufficiently valid from a scientific point of view to be taken into account for their application in Italy is the priority, and not writing new systematic reviews.

Based on these considerations, the production of these Recommendations included the following operational phases:

- Identification of expert drafters
- Identification of systematic reviews and the most recent guidelines published on the topic
- Formulation of clinical themes (Annex 1) used to develop the guidelines
- Definition of recommendations by individual drafters through their response to the identified clinical themes
- Definition of the recommendations grading by the group of expert drafters

Specifically, the Quality Level and the strength of these recommendations were graded and expressed in Roman numerals (I to VI) and in letters (A to E). The Quality Level refers to the likelihood that a certain amount of knowledge derives from studies planned and conducted in such a way as to produce valid information without systematic errors, while the Strength of Recommendation refers to the likelihood that the practical application of a recommendation will lead to an improvement in the health status of the target population to which the recommendation is addressed.

The Level of Quality and Strength of Recommendations were defined according to the criteria suggested by the Methodological Manual of the National Guidelines System (**table 1**).

To develop these phases, an operational meeting was organised during the SIGO-AOGOI-AGUI National Congress, followed by an exchange of material and comments via email.

The Recommendations approved by a majority of the Group of Drafters have been revised by the Auditors appointed by the three Scientific Committees.

A summary of the Recommendations with the relevant level of quality and the strength of the recommendation is provided in Annex 2.

Table 1.
Quality level and Strength of the Recommendations - Grading. From: ISS-PNLG 2002

	QUALITY LEVEL
I	Evidence obtained from multiple randomised controlled trials and/or systematic reviews of randomised trials.
II	Evidence obtained from a single randomised study of adequate design.
III	Evidence obtained from non-randomised cohort studies with concurrent or historical controls or their meta-analysis.
IV	Evidence obtained from retrospective case-control studies or their meta-analyses.
V	Evidence obtained from case studies («case series») without a control group.
VI	Evidence based on the opinion of authoritative experts or expert committees as indicated in the guidelines or consensus conferences, or based on the opinions of the members of the working group responsible for these guidelines.
	STRENGTH OF THE RECOMMENDATION
A	The execution of that particular procedure or diagnostic test is strongly recommended. It indicates a particular recommendation supported by good quality scientific evidence, even if not necessarily type I or II.
B	There are doubts about whether that particular procedure or surgery should always be recommended, but it is believed that its execution should be carefully taken into account.
C	There is substantial uncertainty in favour of or against the recommendation to perform the procedure or surgery.
D	The execution of the procedure is not recommended.
E	The execution of the procedure is strongly discouraged.

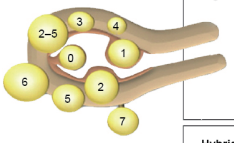
RECOMMENDATIONS

BACKGROUND

Uterine fibroids are benign, gynaecological tumours with the greatest incidence and prevalence and are the main cause of hysterectomy.[1] After the age of 50, it is believed that their prevalence is around 70 to 80%.[2] They are caused by abnormal monoclonal growth of smooth muscle cells and connective matrix and respond to hormonal stimuli. They look like roundish, often poly-lobed fleshy masses, with a firm-elastic texture, and are separated from the surrounding myometrium by reactive connective tissue which is arranged to form a real pseudocapsule. The terms fibroids, myomas, leiomyomas or fibromas are used interchangeably. They do not respond to the rules of Mendelian inheritance, but a sort of inheritance for this pathology is well known; the etiopathogenesis remains unidentified, but known are risk factors, such as premature menarche, nulliparity, African ethnicity, obesity, polymenorrhea, arterial hypertension and diabetes.[1,3] Symptoms are closely related to the number, position and size of fibroids. Small ones, especially isolated and subserosal, are often asymptomatic. The most common disorders include abnormal uterine bleeding, pelvic pain, infertility, urinary and intestinal disorders due to the compression on these regions.[4] They can get larger under the action of ovarian steroids (estrogen and progesterone) or can be stable for all the woman life. The action of progesterone is mediated by estradiol which, through its ERα receptors, induces the expression of progesterone-specific receptors in smooth muscle cells, then progesterone regulates the genes involved in cell proliferation and apoptosis.[5]

Usually fibroids are divided into 3 classes, according to their position in the uterus: intramural fibroids, if they grow within the muscular uterine wall; submucosal fibroids, if they are on the inner surface of the uterus; and subserosal fibroids, if they modify the external profile of the uterus. These three classes are not so well defined in clinical practice, and it is not rare to observe fibroids in intermediate positions. The recent FIGO classification system (figure 1) takes into account every kind of location and divides fibroids into 10 different classes.[6] It is a common belief, even among specialists, that fibroids can grow rapidly during pregnancy, but the most numerous cases in the literature do not confirm this belief,[7-8] indeed, according to them, there may even be a decrease in their diameter during gestation and, even in the presence of fibroids, the risk of possible obstetric complications can be considered as low.[9] However, multiple and large fibroids can change the maternal-fetal outcome, since they increase the risk of fetal malposition, premature delivery, placental abruption, placenta previa, premature rupture of the membranes, retained placenta, post-partum haemorrhage, and caesarean section.[10] Regarding the rate of neoplastic degeneration of fibroids, it is not yet well known whether leiomyosarcomas and muscle tumours with uncertain malignancy (STUMP) originate predominantly from fibroids. Their incidence, however, is very low (0.22-0.49%) and certain diagnostic criteria have not yet been identified.[11-13]

Figure 1.
FIGO (International Federation of Gynecology and Obstetrics) leiomyoma subclassification system.
Note: Reprinted from Int J Gynaecol Obstet. Vol 113 (1). Munro MG, Critchley HO, Brodes MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. pp.3-13. Copyright 2011, with permission from Elsevier[1].



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

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SECTION 1: DIAGNOSTIC FRAMEWORK

1.1 Ultrasound

In recent years, ultrasound, Colour-Power Doppler Fluximetry and three-dimensional approaches have greatly improved the diagnosis of uterine fibroids, and consequently made a more targeted surgical management possible, also thanks to the contemporary development of minimally invasive surgery techniques.

In the common ultrasound practice, leiomyomas or uterine fibroids must be distinguished from adenomyosis and from rare myometrial malignant pathologies (leiomyosarcomas), which still poses considerable problems of differential diagnosis.

The ultrasound evaluation of a uterus with uterine fibroids can be performed either with transvaginal probe or with a transabdominal probe, or with both of them, depending on the size of the uterus that should be assessed before the ultrasound examination with a bimanual examination.

A transabdominal approach is recommended with 3.5 to 7.5 MHz Convex probes in case of large and/or uterine fundus fibroids; a full bladder examination may help, but is not essential. The transvaginal pathway is more useful in case of smaller intramural and submucosal fibroids; the current availability of multi-frequency probes (4.5 to 10 MHz) associated with the possibility of changing the position of the channel, allows a satisfactory evaluation of the majority of fibroids.

1.1.1 What are the ultrasound aspects of uterine fibroids and what are the methods used for a correct medical report?

The ultrasound appearance of uterine fibroids is a roundish mass, which can be hypoechoic or hyperechoic, based on the amount of smooth or connective muscle component.[1,2]

Echogenicity is variable and there may be some hyperechogenicity within the lesion. The *edges* are usually clear, often hyperechoic, well differentiated from the surrounding myometrium. Using colour or power Doppler, a circumferential flow around the lesion can be observed.[2] In the case of fibromatosis characterised by multiple nodes, the uterine body shows irregular contours and often not well recognisable edges. As for pedunculated fibroids, careful evaluation of the ipsilateral ovary and its anatomical integrity may aid the differentiation between them and solid neo-formations of ovarian origin. Leiomyomas positioned laterally, especially if in the cervico-isthmic region, may occur in relation to the broad ligament; to differentiate them from pedunculated subserosal fibroids, it may be useful to evaluate their mobility with respect to the probe and the surrounding tissues. Ultrasound examination of fibroids shall be used to assess: location, size, number, echo-structure and vascularity, growth and mobility and consistency of fibroids.[2,3]

Location

To properly identify where fibroids are located, the uterine version must be taken into account. Longitudinal scans of the uterine body allow to better assess the anterior or posterior position of fibroids, while transverse scans identify its lateral position.

The location of fibroids should be reported using the FIGO classification: 0= interstitial pedunculated; 1= submucous, < 50% intramural; 2= submucous, ≥ 50% intramural; 3= 100%

intramural, but in contact with the endometrium; 4= intramural; 5= subserous, ≥ 50% intramural; 6= subserous, < 50% intramural; 7= subserous pedunculated; 8= others (cervical, parasites).[4] Subserosal fibroids usually deform the external uterine profile, while intramural fibroids, especially small in size, do not. Larger intramural fibroids frequently have a subserosal or submucosal position, or even both (transmural). Intramural fibroids in position 3 to 5 of the FIGO classification may deform the junctional area. The coronal section obtained with 3D ultrasound examination appears very useful for this evaluation.[2]

In case of submucosal position, the endometrium is dislocated and the image of the endometrial line is deformed; fibroids with a marked intracavitary component interrupt the ultrasound image of the endometrial line. The quantification of the intracavitary and intramural component of a submucous fibroid can be assessed with greater sensitivity by intracavitary saline infusion (sonohysterography).[2]

This method allows a better identification of submucous fibroids and by measuring the area of the intramural and intracavitary component of the fibroid, allows to accurately evaluate their grading (0, 1, 2 of the FIGO classification). In the case of submucous fibroids, the evaluation of the free myometrial margin behind the fibroid is also recommended, although according to some hysteroscopists, this measure is not always necessary.[5,6]

Size and number

To measure the fibroids, it is necessary to place gauges on the external contour of the formation (capsule) and the measurement should be performed on the three axes for volumetric assessment, which can be particularly useful to monitor fibroids growth during the follow-up.

It is advisable to specify the number of displayed nodes, even if in the presence of multiple, intramural or subserosal small fibroids, this data does not have particular clinical significance.

Echostructure

The echostructure of fibroids is quite variable, sometimes less echogenic than the surrounding myometrium, but usually more echogenic, due to the presence of diffuse hyperechoic echoes. Fibroids have a hyperechoic pseudo-capsule, which is variable, depending on the amount of smooth and connective fibromuscular tissue. Echogenicity can be regular (homogeneous and/or characterised by a symmetrical pattern of echogenicity: hypoechoic, isoechoic or hyperechoic) or irregular (heterogeneous), due to mixed echogenicity or due to the presence of echogenic areas or cystic areas (regular or irregular).[2] Anechoic areas can be differentiated from large vessels using power Doppler ultrasound, in order to confirm the absence of blood flow. Some shadows can originate from the edges of the lesion, and in that case, they are reported as edge shadows, or originate within the lesion and in this case, they are called internal shadows.[2,7] The shadow intensity is subjectively reported as mild, moderate or intense[2]. Fan-shaped shadow is defined by the presence of hypoechoic linear striae, sometimes alternating with hyperechoic linear striae. In the presence of calcific degeneration of the fibroid, the capsule can be very hyperechoic and/or the presence of internal hyperechoic areas with formation of back shadows can be observed. Sometimes the shadow can be so large that the back edges of the fibroid cannot be evaluated.[2]

Inside the fibroids, some anechoic areas with irregular contours can be observed, these are areas of colliquative necrosis. Spontaneous colliquative necrotic degeneration may occur in the case of rapid growth of the fibroid, red degeneration is the initial manifestation on the days following ischemia. The ultrasound appearance of red degeneration may not be consistent, although in some case it has been described as a homogeneous lesion characterised by low echogenicity, hyperechoic edges and by the absence of the internal vascularity.[8,9] Haemorrhage and oedema, may appear with ultrasound in mixed echoic tumours. Hyaline degeneration with mixed echogenicity and a reduction of the consistency of fibroids, as well as in their volume, these characteristics can be observed during therapy with GNRH analogues or with Ulipristal Acetate. After ischemia induced by conservative treatments, fibroids are often homogeneous, hypoechoic and characterised by hyperechoic edges and acoustic shadows.[10,11] Usually there is no internal vascularity, but few irregular vessels can be observed. Cystic or myxoid degeneration may develop resulting in a hypoechoic cystic area with a fluid or myxoid content.

Vascularity

Colour or Power Doppler sonography should evaluate the distribution, progression and number of fibroid vessels.

Power Doppler is usually preferred to Colour Doppler, because it allows to better identify small vessels with a low flow rate. Colour Doppler is used to assess the direction of blood flow. The Colour or Power Doppler box should include the whole fibroid. Magnification and setting should be

adjusted to ensure maximum sensitivity and the Doppler spectral gain should be reduced until all artefacts disappear. Usually, the settings that allow to detect blood flow rates of 3 to 9 cm/s are ideal, but this may change based on the characteristics of the ultrasound device used. Fibroids can be characterised by circumferential, internal or mixed vascularity. The term "circumferential" refers to those vessels that surround a fibroid in the capsule, while the vessels located within the fibroid are defined as intralesional or central vessels.[2,12,13]

Usually, the vascularity of fibroids is greater in the capsule and less in the central region, with vessels radially arranged. The extent of vascularity is likely to vary according to the growth rate of the tumour. The degree of vascularity should be reported using a subjective colour scale, with a score of 1 representing the absence of colour and a score of 4 representing a remarkable colour signal. This score is based on a subjective assessment of both the lesion vascularity rate and the colour tone. The colour score can be assigned to the fibroid separately for the capsular and the central vascularity.[2] For research purposes, the flow of colour within a lesion can be quantified using 3D ultrasound with virtual computer-aided analysis (VOCAL), in order to calculate 3D power Doppler indices: the vascularity index (VI, the number of voxels in the volume expressed as a percentage of the total number of voxels in the volume, potentially reflecting vascularity); the flow index (FI, the average colour value in the colour voxels expressed as a number from 0 to 100, potentially reflecting the flow rate); the vascularity flow index (VFI, calculated by multiplying the VI by the FI, reflecting the average colour of all voxels expressed as a number from 0 to 100 and potentially reflecting tissue perfusion).[14] Since 3D vascular indices depend on ultrasound settings, their reproducibility in clinical practice remains doubtful and their use must be adequately studied. As long as these indices are not exceeded, we recommend using them only for specific research projects.[15]

Power Doppler may also help to better assess the direction of the vessels and therefore aid the differentiation between fibroids and adnexal masses. Usually, a solid adnexal neo-formation shows diffuse irregular vascularity, while fibroids, as previously described, are mainly characterised by peri-capsular vascularity. This distribution also aids differential diagnosis with endometrial polyps for which a vascular axis can be easily identified.[16]

Recommendation	Evidence level	Strength of recommendation
Ultrasounds are a safe and accurate diagnostic technique for uterine fibroids assessment.	III	A
Medical ultrasound allows to identify the presence of a fibroid, but also to evaluate its location, size and degree of vascularity.	III	A
An ultrasound classification of fibroids helps to assess if surgery is required and surgical obstacles.	III	B

1.1.2 What are the main aspect of differential diagnoses of uterine fibroids?

1.1.2.1 Adenomyosis

Distinguish between fibroids and diffuse or focal adenomyosis or adenomyomas is extremely important for the correct medical and surgical treatment. In addition to the symptoms, there are different ultrasound characteristics.

Adenomyosis is caused by the proliferation of endometrial glands and stroma that form a poorly defined lesion within the myometrium. On histological examination, adenomyosis is classified as diffuse when the endometrial glands and the stroma are widely distributed in the myometrium, while focal adenomyosis is when they are identified as nodular aggregates.[17] Focal adenomyosis is different from adenomyoma. An adenomyoma is defined by pathologists as focal adenomyosis with compensatory hypertrophy of the myometrium surrounding the lesion.

The ultrasound characteristics of adenomyosis should be reported and quantified.

In particular, transvaginal ultrasonography shows that adenomyosis is characterised by:[2,18-22]

- Increased size of the uterus, without clear evidence of any formation, with poorly definable lesions, characterised by asymmetric thickening and globular shape of the organ;
- Diffuse heterogeneous myometrial echo-structure characterised by the presence of areas of increased or reduced echogenicity;
- Hypoechoic linear myometrial striae defined as subtle radial acoustic shadows that do not come from echoic areas or leiomyomas;
- Myometrial cysts defined as anechoic circular areas;
- Alteration of the junctional area assessed by 3D ultrasound.

In particular, the presence of myometrial cysts in a poorly defined area has the highest specificity for diagnosis,[18] however these are only present in 40 to 60% of cases.[20] Furthermore, the combination of myometrial cysts and hypoechoic linear striae makes the ultrasound examination even more accurate.[23]

The use of the Power Doppler (PD) technique is also useful for diagnosis purposes and aids the differentiation between adenomyosis and uterine fibroids.[2]

Indeed, in case of adenomyosis, PD shows radially distributed vessels within the affected myometrium that follow their normal path perpendicular to the endometrial interface while, in case of fibroids, it shows a prevalently peripheral, capsular vascularity, with only a few vessels getting into the centre of the fibroid. Furthermore, for fibroids, ultrasound shows the presence of a pseudocapsule that separates them from the surrounding tissues, a characteristic that cannot be found in case of adenomyosis.[2]

1.1.2.2 Leiomyosarcoma

There are few evidences related to a diagnosis of uterine leiomyosarcoma with ultrasound examination and they mainly refer to numerically inconsistent retrospective studies, which make not possible to define final guidelines. There are also other rare uterine tumours deriving from smooth muscle other than leiomyomas but, to date, only limited informations on their ultrasound characteristics have been reported.[13,24-26] However, this aspect has become incredibly relevant in view of the discussion about when, or whether, fibroids can be morcellated during laparoscopic surgery.

Uterine leiomyosarcomas are pure myometrial lesions and are typically single and large tumours. Macroscopically, leiomyosarcomas are very variable, being intra-myometrial formations consisting of a greyish parenchyma with many haemorrhagic and necrosis areas, a formation that protrudes into the uterine cavity similar to a polypoid or, in the case of well-differentiated tumours, very similar to a leiomyoma. Histologically, the differential diagnosis between a well-differentiated leiomyosarcoma and a leiomyoma can be difficult, and is based on the degree of mitotic activity, cellularity and pleomorphism. Their ultrasound characteristics may not be distinguished from those of normal fibroids or may appear as an irregular vascular mass with a regular or irregular contour often with irregular anechoic areas caused by colliquative necrosis.[12,13]

Ultrasound elements for a possible diagnosis of leiomyosarcoma may be: the presence of a large single fibroid, the presence of many and large areas of colliquation and wide neovascularization especially at the central level.[2,13,24-26] Other ultrasound elements may include rapid growth and invasion of the nearby organs.[27]

Recommendation	Evidence level	Strength of recommendation
Ultrasound is an accurate diagnostic technique for the assessment of adenomyosis.	III	B
Ultrasound allows to verify the presence of adenomyosis, but also to evaluate its different types (diffuse or focal adenomyosis, adenomyoma).	IV	B
An ultrasound classification of adenomyosis may be useful but is not yet available.	VI	C
Medical ultrasound is an accurate diagnostic technique for the diagnosis of leiomyosarcomas.	IV	C
Medical ultrasound is an accurate diagnostic technique for the diagnosis of other uterine myometrial tumours.	IV	C

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1.2 MRI

Magnetic Resonance Imaging (MRI), thanks to advancements in technology, has improved its diagnostic performance and tissue characterisation. Compared to medical ultrasound, MRI offers large fields of view (FOV), multiple planes, high contrast resolution of T2 mapping, multiple parameters and post-contrast graphic behaviour.[1,2]

Leiomyomas are generally observed as defined lesions with hypointense signal in T2-weighted sequences and isointensity images, compared to the myometrium, in T1- weighted images.

However, these aspects, in case of degenerative phenomena, can change with loss of the characteristic signal, making differential diagnosis of leiomyoma difficult, in particular between lesions such as mesenchymal mixed tumours (MMT), smooth muscle tumours of uncertain malignant potential (STUMP) and sarcomas.[3]

MRI is a second level diagnosis technique. The main indications are [1,2]:

- *Fibroids with atypical clinical or ultrasound features,* such as rapid growth, blood loss, pain, echostructure or atypical vascularity, etc.;
- *Voluminous lesions wich the origin is defined as*

uncertain after ultrasound examination;

- *Evaluation before and after treatment in patients that must be treated with embolization or Focused Ultrasound (FUS*)

1.2.1 MRI Protocol

MRI examination should be performed with equipment equipped with a 1.5 T magnet and, using a multi-channel phased-array coil after intravenous administration of some antiperistaltic agents and after 6 hours of fasting.

The standard MRI protocol for the study of leiomyomas includes, as a first sequence, the acquisition on the coronal plane of a large field of view with T2-weighted sequences (which allows to evaluate the size of the uterus) the position of the fibroids, the type of fibroids and the presence of secondary signs, such as ascites effusion and/or hydroureteronephrosis, etc.

After an initial classification, a targeted study will be conducted with T1 and T2-weighted high resolution morphological sequences with and without Fat Saturation (FS), as well as a post-contrast graphic study, and Diffusion sequences have also been recently included (DWI).

The morphological study, and in particular T2 sequences, thanks to a high contrast resolution, allow to evaluate the site, the number, the involvement of the endometrial cavity and the adjacent organs and the presence of overlapping degenerative phenomena, such as cystic degeneration, hyaline and myxoid degeneration. Red degeneration is well visible in T1 sequences without and with abatement of the adipose signal.[4]

Diffusion sequences are expressed by the free movement of water molecules, the so-called Brownian motion, within the tissue. These sequences were mutated by neuroradiological imaging for the study of acute stroke, being able to identify the ischemic lesion early, when Computed Tomography (CT) is still negative. Diffusion sequences, in addition to offering a qualitative assessment (hypo-signal or hyper-signal) may also provide a quantitative parameter (Apparent Diffusion Coefficient or ADC).

In recent years, these sequences have also been used in body experience evaluation, in oncology, as they are able to reflect the cellularity of a tissue, and are used as a routine evaluation method for some lesions, such as such as prostate or cervical cancer, both for staging and for post-therapy re-evaluation. It is recommended to acquire DWI sequences with multiple values of b (b0, b1000), a factor that expresses the degree of diffusion and the following calculation of the ADC.

The use of an intravenous contrast medium, at a dose of 0.1 mmol/kg of gadolinium chelates, is a mandatory step for the evaluation of vascularity, type of enhancement, and to document any areas of necrosis and to identify the peripheral pseudocapsule.

Fibroids generally show a synchronous enhancement with the myometrium. This information is extremely important, for example in esophytic, voluminous lesions of uncertain origin. In this case, post-contrast graphic sequences help to assess the enhancement level and to identify the vascular peduncle. Fibroids, also in relation to the hormonal status of the patient and to any hormonal therapies, may show a hyper or hypo-vascularization and usually also a homogeneous impregnation of the contrast medium.[1]

The presence of large areas of necrosis is an important element for diagnosis because they are quite evident in lesions, such as STUMP or Sarcomas.

T1-weighted sequences with Fat Saturation (FS) on axial and/or sagittal planes are used. Currently, dynamic or perfusion studies have been suggested.

Dynamic studies provide important informations about post-contrast graphic behaviour.[5] In this case, a sequence train is repeated for about 6 times with a total time of about 3 minutes, which may vary also based on the equipment used.

As for perfusion studies, these have not yet been employed in clinical practice and, at the moment, there are no literature data on their actual diagnostic performance unlike other segments such as the breast, the brain and the prostate.

1.2.2 Key MRI aspects of fibroid degeneration

The signal of fibroids in MRI varies according to their histological characteristics.

Typical non-degenerated fibroids consist of connective tissue and smooth muscle cells determining that typical hypo-intensity shown by T2-weighted images and isointensity in T1- weighted images with the myometrium, as already reported.

In the case of rapid growth, the lack of intralesional vascularity can cause a change in the structure with degenerative effects.[4]

Hyaline degeneration is the most common type of degeneration and is not always accompanied by a change in the signal described. In the presence of calcifications, there will be no enhancement in relation to the extent of the calcification rate.

Cystic degeneration leads to an increase in the

signal intensity of T2-weighted images, which will be directly proportional to the extent of inclusion cysts within the fibroid, and T1 basal images will show a consensual hypo-intensity. After administration of the contrast medium, the cyst does not show any enhancement.

Myxoid degeneration shows an increase in the fibroid signal strength and is associated with mild enhancement. Necrotic fibroids show a variable signal in T1 images, and generally hypo-intensity in T2 images; after administration of the contrast agent, total absence of impregnation is observed.

Red degeneration, which corresponds to haemorrhagic infarction, is characterised by an increase in signal intensity in T1 images with FS.

In some cases, leiomyomas can be surrounded by high T2 signal rims, which express a dilatation of the lymphatic and venous vessels, but are not pathognomonic.[6]

Typical fibroids identified by DWI usually have a characteristic effect called "black out effect", characterised by hypo-intense signal in both, low b value images and high b value images, with a corresponding hypo-intensity in ADC.

The presence of areas of hyaline, myxoid or necrosis degeneration may lead to false shrinkage phenomena with consequent problems of differential diagnosis between hyper-cellular fibroids, STUMP and sarcomas. In fact, some components such as blood, fat, melanin and necrosis can determine Pitfalls. It should be pointed out that, in case of hyper-intense signal in DWI sequences with high b value (b1000), the image obtained must be compared to the ADC map. The presence of hyper-intensity on the map is an expression of the "T2 Shine Through" effect, while in the case of hypo-intensity on the maps, a quantification of the ADC should be considered. Some authors report suspected ADC values below 1.1 mm^2/sec, but for such values there are fibroid overlaps.[7] However, it should be emphasized that, for the characterisation of fibroids, all the parameters must be considered, including morphological aspects (T1 and T2), DWI sequences and type of enhancement, and must be correlated with clinical practice. Therefore, a non-homogeneous hyper-intense fibroid in T2 images, with signs of shrinkage in DWI and necrosis areas must be carefully evaluated together with further signs such as edges, relationships with surrounding structures, the presence of lymphadenopathy and the presence of ascites[7].

Moreover, high b value DWI images, help detect lymph nodes and evaluate peritoneal carcinosis.

1.2.3 Lesions of uncertain origin

MRI indications for fibroid evaluation include the classification of masses of uncertain origin. In this case, a multi-planar study finalised in a better investigation of the ovaries, the vascular peduncle, the relationship between the mass and the uterus with cleavage planes is always required.

1.2.4 Evaluation before and after treatment

The assessment before and after treatment with MRI-guided Embolization of the uterine arteries (EAU) and focused ultrasound (FUS) must focus on fibroid location, structure, size and involvement of the surrounding structures, with regard to FUS. Therefore, accurate mapping is necessary.

In the selection of patients to submit to FUS, ineligibility criteria include, in particular, pedunculated subserosal fibroids and high T2 signal fibroids. Evaluation in relation to the surrounding structures (intestinal loops and sacral promontory) is extremely important; fibroid size is not a contraindication, since even fibroids larger than 5 cm can be treated.[8]

After treatment with FUS, fibroids usually show a shrinkage ranging from 20 to 50%, and after administration of the contrast agent, absence of enhancement is reported in relation to coagulative necrosis. The non-perfused volume (VPN) of the myoma, then, proves that the treatment was successful. The persistence of fibroid perfused portions is a possible indicator of relapse.[8,9]

Selection of patients that can be treated with MRI-guided EAU, includes the following parameters:[10]

- size (lesions up to 13 to 15cm can be treated);
- location (fibroids which are mainly sub-mucous are associated with a risk for possible post-treatment complication; pedunculated fibroids are considered as a relative contraindication for peduncles smaller than 2cm);
- signal intensity in T2- weighted images;
- enhancement: post-contrast graphic behaviour is essential to establish the indication. Fibroids with poor vascularity show poor response to treatment.

After treatment, in addition to the fibroid size, volume, (reduced) T2 intensity signal, location and enhancement must be considered.[11]

In some cases, after treatment with FUS or EAU, expulsion into the endometrial cavity can be observed.

1.2.5 Differential diagnosis

The main differential diagnosis is between adenomyosis and sarcomas:

ADENOMYOSIS

Adenomyosis is frequently associated with fibroids with rates ranging between 30 and 80%. MRI shows high sensitivity and specificity, with values of about 65 and 98%, respectively. Generally, adenomyosis appears as a lesion with undefined edges and with little mass effect.[12]

The basic criteria for the diagnosis of adenomyosis are the following.[13,14]

- Lesion characterised by blurred hypotensity, which is hard to define with cystic areas by T2- weighted images;
- Increased thickness of the endometrial line (>12 mm) with blurred margins;
- Sub-endometrial cystic formations well visible in T2- weighted images;
- Hypointense linear striae in T2- weighted images with involvement of radial myometrium arteries;
- Asymmetry of uterine walls;
- Areas of hyperintensity in FS T1 images (a highly specific but inconsistent sign related to the presence of stromal areas).

It should be pointed out that the aspects described may vary according to the patient's hormonal status and, therefore, during treatment.

SARCOMAS

Differential diagnosis can be complex. Recently, a multi-parameter study with the development of a PRESS score (PRE-operative Sarcoma Score) with the combination of multiple parameters, including the evaluation of the T2 signal, DWI and post-contrastographic behaviour, has been recommended. However, multivariate analysis shows the inconsistency of such data.[15]

Generally, a leiomyosarcoma appears as a single mass with irregular edges with high to medium T2 signal. Extensive necrotic areas are observed after administration of the paramagnetic contrast agent. A haemorrhagic component can be identified in pre-contrast T1-weighted images.[15,16,17]

DWI shows a high signal for values of b 1000 with ADC maps with values between 0.791 and 1.17 $10^{-3}mm^2/s$ [7].

Muscle tumours with uncertain malignancy (STUMP) show similar MRI aspects and their diagnosis is histological.

The identification of possible secondary signs (infiltration of surrounding structures, venous thrombosis, lymphadenopathy, ascites, peritoneal diffusion, hydroureteronephrosis) is essential in case of suspected sarcoma.

Recommendation	Evidence level	Strength of recommendation
MRI is a II level examination for the study of the pelvis.	I	A
MRI for the study of fibroids allows to evaluate their location, size and structural characteristics.	III	A
MRI can aid diagnosis differentiation between fibroids and leiomyosarcomas.	III	B

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1.3 Hyseteroscopy

1.3.1 What characteristics of uterine fibroids can be better studied with hysteroscopy?

It has been shown that ambulatory hysteroscopy, in addition to ascertaining the presence of sub-mucous fibroids, also allows to evaluate important parameters used to assess whether hysteroscopic surgery is required or not:[1-2]

- Location: sub-mucous fibroids may affect the upper 1/3 region, the middle 1/3 region or the lower 1/3 region of the uterine cavity; sometimes they can also develop in the corneal regions and interfere with the lumen of the utero-tubal junction. It should be specified the fibroid location, with respect to the uterine walls, if there is a fundus, back or front or cervico-isthmic localisation.
- Size: the size can be assessed subjectively in relation to anatomical landmarks, such as interstitial distance, or in relation to the dimensions of miniaturized instruments (pincers, scissors, electrodes) introduced into the uterine cavity through the operative channel of modern surgical hysteroscopes. Experience shows that the size of the fibroid is not important as an absolute criterion for surgery, requiring, with expert hands, only extended surgical times.
- Texture: it is evaluated indirectly by exerting pressure on the formation with the distal end of the hysteroscope or with the tip of surgical instruments. Fibroids are usually hard, but in case of haemorrhagic infarction or ischemic necrosis, they may be soft, thus making differential diagnosis between fibroids characterised by degeneration (hyaline, colliquative or adipose) and leiomyosarcomas difficult.
- Depth of myometrial invasion: evaluated by the study of the angle formed by the fibroid's margin and the endometrium (the more acute is the angle, the less the extension of the fibroid inside the uterine wall and vice versa).
- Surface vascularity: on the surface of the fibroid, mainly thin sinusoidal vessels can be observed, the rupture of which can contribute to the bleeding frequently reported by the patients.
- Features of the surrounding endometrium.
- Presence of any associated pathologies (e.g.: polyps, endometrial hyperplasia, adenomyosis).

Many studies in the literature have evaluated the accuracy of hysteroscopy for the diagnosis of sub-mucous uterine fibroids.[3-8] Most of these compared the diagnostic accuracy of hysteroscopy (HSC) versus trans-vaginal ultrasound (TVU), nuclear magnetic resonance (RMI) and sonohysterography.

In 1991, Fedele showed that HSC and TVU had substantially comparable diagnostic accuracy (100% sensitivity for both TVU and for HSC; specificity: 94% TVU vs 96 % HSC); he also concluded that the mapping of uterine fibroids was more accurate with transvaginal ultrasound.[6]

However in 2001, Dueholm pointed out that sonohysterography and MRI are the most precise methods of identification of submucous fibroids, and that MRI is better than other diagnostic techniques for the evaluation of the exact intramural portion of fibroids.[3] Soares and his collaborators have also compared the accuracy of sonohysterography and trans-vaginal ultrasound

for the diagnosis of uterine diseases, confirming that diagnostic hysteroscopy is the gold standard.[8] Therefore, a clear superiority of one of the diagnostic techniques available in the diagnostic accuracy of submucous uterine fibroids was not demonstrated.

Recommendation	Evidence level	Strength of recommendation
Hysteroscopy is a safe and accurate diagnostic technique for the evaluation of sub-mucous fibroids.	III	B
Ambulatory hysteroscopy not only allows us to ascertain the presence of a sub-mucous fibroids, but also to evaluate their location, size, texture and degree of myometrial invasion.	III	A

1.3.2 What is the role of ambulatory hysteroscopy in the pre-surgical assessment of fibroids?

Since the intramural extension of submucous fibroids can vary considerably, influencing the possibility of obtaining a complete resection, a preoperative hysteroscopic classification of submucosal fibroids has become indispensable since the dawn of resectoscopic surgery, in order to highlight the lomitation of a possible hysteroscopic surgery. The classification suggested by Wamsteker et al. (1993)[9] and then adopted by the European Society for Gynaecological Endoscopy (ESGE), which takes into account only the depth of myometrial invasion of submucosal fibroids, is still the most widely used:

- Classification 0 (G0): fibroids entirely developed inside the uterine cavity, pedunculated or with limited implantation base.
- Classification 1 (G1): fibroids with partial intramural development. Intracavitary component of the fibroid >50%.
- Classification 2 (G2): fibroid with prevalent intramural development. Intracavitary component of the fibroid <50%.

Lasmar et al. (2005)[10] have proposed a new preoperative classification of submucous fibroids that considers not only the depth of myometrial invasion, but also additional parameters, such as the extension of the fibroid base with respect to the uterine wall, the size (cm) and the topography in the uterine cavity. A 0 to 2 score is attributed to each parameter and, based on the score, patients are classified into three groups:

- 0 to 4 score (Group I): low complexity hysteroscopic myomectomy;
- 5 to 6 score (Group II): High complexity hysteroscopic myomectomy (consider preparation with GnRH analogues or two surgical steps);
- 7 to 9 score (Group III): consider a non-hysteroscopic surgical alternative.

A recent multi-centre study by Lasmar et al. (2011)[11] has shown that the above classification allows, with respect to the ESGE classification, a greater correlation with the possibility to remove fibroids, completely or not, by resectoscopic myomectomy.

Recommendation	Evidence level	Strength of recommendation
A hysteroscopic pre-surgical classification of sub-mucous fibroids is important to evaluate the operability and degree of surgical difficulty.	III	B

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SECTION 2: MEDICAL TREATMENT

There are many pharmacological strategies that can be used in the treatment of symptomatic uterine fibroids. Medical strategies have traditionally included medications that can control symptoms with specific action on the endometrium, such as estroprogestinic therapy and progesterone, or a dual action on the fibroids and on the endometrium, inducing a menopausal-like state, such as GnRH analogues. Ulipristal Acetate (UPA), a selective modulator of progesterone receptors (SPERMS), and the only drug with specific indication for the long-term treatment of symptomatic uterine fibroids was available in Europe in 2014.

In case of failure of medical therapies, the use of surgical techniques and alternative techniques may be indicated.

2.1 SPRMS (Selective Progesterone Receptor Modulators)

SPRMs are molecules able to bind progesterone receptors with agonist, antagonist or mixed effects on a responsive tissue.[1]

Many molecules belonging to this category have been studied, but randomized controlled trials (RCTs) are only available for two of them.

2.1.1 Mifepristone

Mifepristone (RU-486) has a pure antagonistic action that, as evidenced by a meta-analysis of 11 RCTs of 2013, it induces a statistically significant volumetric decrease of both, the uterus and the lesion, in addition to a relief of fibromatosis associated symptoms.[2]

Mifepristone is effective in reducing bleeding, pain associated with fibroids, and their size.[3] The dose and posology suggested by the authors is 2.5 mg per day for three to six months. The efficacy of mifepristone in the treatment of uterine fibroids has also been demonstrated with doses of 5 and 10 mg for treatment periods of 3, 6, and 12 months by other authors.[4] One study showed that using 10 mg of mifepristone is equally effective as using 25 and 50 mg, with fewer side effects.[5]

A recent multicentre randomized controlled trial compared the efficacy of mifepristone at doses of 10 mg and 25 mg with Enantone 3.75 mg for three months, and showed, in the three groups, the simultaneous decrease in the volume of the fibroids, but fewer adverse events associated with the use of mifepristone, at both the dose of 10 and 25 mg.[6]

Evidence is lacking on the possible relationship between administration and atypical endometrial hyperplasia.

2.1.2 Ulipristal acetate

Ulipristal acetate (UPA) has a mixed agonist-antagonist action on Progesterone receptors with anti-proliferative effect on myomas.

Numerous recent studies identify UPA as the first medical choice for the treatment of fibroids.

In Phase III PEARL 1 and PEARL 2 studies, UPA has proved to be effective in both, bleed control and in reducing the size of fibroids before the surgical treatment. It also proved to be a medication with a good safety profile, even compared to previous reference medications, such as GnRh analogues.[7-8]

PEARL 1 study compared UPA with placebo in the pre-surgical treatment of symptomatic fibroids, showing a volumetric reduction of lesions after thirteen weeks of treatment at a dose of 5 mg, which is the currently marketed formulation, the reduction was of the 21% against the 3% of growth in the placebo group ($P < 0.01$). This effect remains for six months after the interruption of the therapy. The rate of amenorrhea at this dose is 73% and in most women, it occurs after 10 days of treatment.[7]

A second RTC showed a non-inferiority of UPA compared to leuprolide acetate in the control of menorrhagia related to uterine fibroids with symptom control in 90% of cases at a dose of 5 mg versus 89% of cases treated with the GnRH analogues, that however reported major vasomotor symptoms. With the SPRM under study, the average time to amenorrhea is 7 days versus 21 of Leuprolide acetate.[8]

Two RCTs showed the long-term efficacy of UPA. The first trial showed that the intermittent and repeated intake of UPA 10 mg is effective and safe in the control of bleeding and in the volumetric reduction of lesions in women with symptomatic uterine fibromatosis.[9]

The second study evaluated efficacy and safety of the use of UPA at the dose of 5 mg and 10 mg with intermittent administration up to four cycles of three months each one. Both doses were effective in the control of bleeding (>80% for both groups) and in the volumetric reduction of lesions (reduction of 54% for 5 mg and 58% for 10 mg). In both groups, there was a reduction of pain and improvement in quality of life. Less than 5% of the treated patients discontinued treatment due to side effects.[10]

Already after 7 days, UPA normalizes bleeding with a more rapid action compared to GnRHa (about 30 days), and within the first 10 days, the 50% of patients with UPA 5 mg have amenorrhea.[11]

After three months of use, UPA allows, in 90% of cases, to control uterine bleeding and therefore to correct the consequent anaemia also in view of a subsequent surgery. The same study shows that the effect of UPA also has been going on for six months after its suspension, contrary with the use of analogues, which, on the other hand, determine a rapid regrowth after the end of the therapy (rebound effect).

In the vast majority of cases, fibroid shrinkage (≥25% in 80% of patients) and bleeding control (in> 90% of patients) made it possible to avoid surgery and restore haemoglobin level. This therapeutic scheme also showed a clinically significant reduction in fibroid volume from 62.3%, after the first cycle, to 78.1% of patients after 4 cycles, thus suggesting a greater benefit with repeated cycles.[11-12]

In case of a good patient response, the treatment can be interrupted after 4 cycles and patients re-evaluated.

Whether the symptoms should reoccur, medical therapy may be repeated. In this context, the goal is to reach menopause without surgery.[13]

Great attention was paid during phase III studies on the possible adverse effects of the medication and on the effect of this class of medications on the endometrium.

The treatment induces a spectrum of benign endometrial modifications called PAECs (PRM associated endometrial changes) found in about 30% of the treated women.[14]

As shown by PEARL studies, these changes are reduced to less than 30% after only one period and disappear 3 to 6 months after the suspension of the treatment.

The incidence of endometrial hyperplasia in phase III studies, both in the short and in the long term (excluding patients who took NETA to avoid bias), is 0.9%, 0.4% of which shows cellular atypia; these percentages are lower than those found in the control group, confirming its safety profile.[15]

The safety of UPA (5mg/day) has been confirmed by several pharmacokinetic studies with higher doses.[16-17] To date, the results of the studies demonstrate the efficacy of the treatment with 5 mg of UPA and confirm the safety of repeated administrations (4 sequential cycles of 3 months each) for symptomatic fibroids.[13]

The most frequently reported side effects, with the relative incidences of the first, second, third and fourth treatment cycles are: hot flashes in 5.7%, 3.7%, 1.7% and 2.8% of cases, respectively, breast tension or pain in 3.0%, 0.9%, 0% and 0.6% of cases, respectively, headache in 10.0%, 6.0%, 2.1% and 2.2% of cases, respectively. Headache incidence is higher during the first month of treatment. During the PEARL IV study, eight serious side effects were reported: five cases of menorrhagia, one bipolar disorder, one abdominal pain and one low back pain.

In all PEARL studies, blood estradiol levels remained higher than post-menopause, not altering bone mineral density, either at 5 or 10 mg (PEARL II).[9]

In the PEARL III study, the coagulation profile was analysed, which was unchanged after repeated cycles of UPA 10mg.[9] During the PEARL IV study, no routine dosage was performed but no thromboembolic events occurred.[10]

Medical treatment with SPRMs may be very useful, since long-term intermittent therapy (repeated in the event of recurrence of symptoms during the interval) may help to avoid or at least delay surgery.

2.2 GnRH analogues

This class of medications induces a state of relative hypoestrogenism, and, therefore a temporary menopause with amenorrhea, which results in an improvement in haemoglobin levels in those patients with secondary anaemia and a reduction in the volume of fibroids.[18]

GnRH agonists are able to induce a volumetric reduction of fibroids above 50% after twelve weeks of treatment. The duration of the treatment with GnRH analogues is limited to three to six months, due to the hypoestrogenism caused by them, while volume reduction of lesions is only temporary (lesions grow back after only twelve weeks).

An add-back therapy can be added for the control of estrogenic deprivation symptoms.

A prospective randomized study on long-term use (> 6 months) of GnRH agonist medications

associated with estrogen/progestin and progestin contraceptives showed that the addition of contraceptives can reduce the effect on the fibroid volumetric reduction and that with both regimens the loss of bone mass remains significant, approximately 3%.[19-20]

A recent systematic review shows that there is evidence of poor-moderate quality supporting the use of tibolone, raloxifene, estriol, and ipriflavone as an aid in preventing bone mass reduction during treatment with GnRH agonists. Medroxyprogesterone acetate (MPA) and tibolone showed good efficacy in reducing vasomotor symptoms.[21]

The use of GnRH agonists is useful for preoperative patient preparation because it reduces the volume of lesions and anaemia.[22]

Several studies show how preoperative use of GnRh-analogues can improve anaemia before surgery, reduce endometrial thickness and fibroid volume as well as its vascularity with reduction of intraoperative blood loss.[23]

2.3 GnRH antagonists

GnRH antagonists induce a direct blocking mechanism against the hormone receptor with the advantage of avoiding the initial "*flare up*" effect caused by agonists.[24]

In vitro studies show a possible role of this class of medications in controlling the growth of uterine fibroids but, at the moment, there is no evidence supporting their use. [25]

2.4 Oral contraceptives

Oral contraceptives (COCs) were used to control fibroid bleeding. Their effectiveness in treating bleeding is limited and a reduction in the volume of fibroids has never been documented.[26]

There are no studies comparing the effectiveness of UPA with COCs. However, there is a small randomized trial comparing COCs with medroxyprogesterone acetate in women with excessive menstrual bleeding due to any etiology, and treatment with COC has been seen to reduce the bleeding by 88% with an average of 3 days.[27]

The use of COCs in the management of abnormal bleeding due to the presence of fibroids has been evaluated by very few studies. In a recent meta-analysis of cohort studies and case-control studies on this topic, COC treatment was associated with a 17% reduction in fibroid-associated symptoms.[28]

Another observational study compared the use of COCs with placebo and found a significant reduction in bleeding without any changes in the fibroid volume.[29]

Low dose oral contraceptives can reduce menstrual bleeding in patients with uterine fibromatosis less than levonorgestrel-releasing intrauterine system or IUDs (see below).[30]

2.5 Oral progestins and levonorgestrel-releasing IUS

Progestin contraceptives, in addition to induction of endometrial atrophy, have a double biochemical effect on the growth of fibroids: a stimulating effect with the increase of the Epidermal Growth Factor (EGF), and an inhibitory effect with the negative modulation of insulin-like growth factor-1 and the down regulation of estrogen and progesterone receptors.[31]

A prospective study has shown that LNG-IUS (Levonorgestrel-releasing Intrauterine-Systems) significantly reduce blood loss and uterine volume in women with menorrhagia, associated with fibromatosis or not, while they have no effect on the size of the fibroids.[32]

One RCT showed superiority of LNG-IUD in the control of menorrhagia in patients with uterine fibroids compared to combined oral contraceptives.[33]

In a multi-centre randomized trial, the authors found a lower efficacy of Lynestrenol in the volumetric reduction of fibroids, when compared with the efficacy obtained with a GnRH analogue (Leuprorelin depot 3.75 mg).[34]

A systematic review of 2013 on the use of progestin contraceptives and LNG-IUDs concludes that Levonorgestrel-releasing IUDs are effective in the control of uterine bleeding associated with uterine fibromatosis and that oral administration of progestogen contraceptives does not reduce neither the volume of the lesions nor the symptoms associated with them.[35]

2.6 Androgens

The most commonly used androgen for the treatment of uterine fibromatosis is Danazol, which can cause a fibroid volume reduction of 20-25%[36].

A subsequent systematic review did not confirm this action, as there were no randomized controlled trials supporting it.[37]

Because of the modest action and the side effects associated with its use, Danazol should not be used routinely for the management of symptomatic fibroids.[38]

2.7 Aromatase inhibitors

Aromatase inhibitors, including Letrozole,

inhibit the conversion of androgens to estrogens with growth inhibition of uterine fibroids. A systematic review of their use includes only one trial reporting a volumetric reduction of fibroids equal to 46% after twelve weeks compared to 32% obtained with GnRH agonists and minor vasomotor side effects (0/33 vs. 26/27, P < 0.05). Since the data on the volumetric reduction are not statistically significant, there is currently no evidence justifying their use.[39]

2.8 Estrogen receptor antagonists and SERMs (Selective Estrogen Receptor Modulators)

Estrogen receptor antagonists, including Fulvestrant, have shown, in a RCT, lower efficacy compared to GnRH agonists, in term of volumetric reduction and relief of bleeding due to fibroids.[40]

SERMs are selective modulators of estrogens receptors with non-steroidal composition characterised by a specific agonist or antagonist action. Raloxifene is the most used of these drugs for the treatment of uterine fibromatosis; despite this, there are still few studies on its use as a single-agent.[41]

Recommendation	Evidence level	Strength of recommendation
Medical therapy is able to control the symptoms. On the other hand, its effectiveness in reducing the volume of fibroids in the long term has not yet been well defined.	I	A
Recent studies identify Ulipristal Acetate (UPA) as the first medication for the treatment of symptomatic uterine fibroids.	II	A
The efficacy of oral contraceptives (COC) for the treatment of fibroid symptoms is limited and a reduction in the volume of fibroids has never been documented.	III	B
LNG-IUS significantly reduces blood loss and uterine volume in women with menorrhagia, associated or not with fibromatosis, while having no effect on the size of the fibroids.	III	B
GnRH agonists are able to induce a volumetric reduction of the fibroma of more than 50% after twelve weeks of	I	A

✓ **<u>What is the medical treatment for fertile women with symptomatic type 2 to 5 uterine fibroids?</u>**

1. <u>Women who desire pregnancy</u>

In the case of a type 2 fibroids, a therapy with UPA can be proposed in order to reduce the size of the lesion before hysteroscopic myomectomy (that must be planned after the first menstrual bleeding) or even to obtain a volumetric reduction, so that the uterine cavity is no longer deformed and surgery is no longer required.[9-10,42-46]

In case of multiple fibroids or different types of fibroid (2 to 5), at least two treatment cycles for three months should be suggested, after which, based on the patient's response, clinical options must be modulated.[10,42-47] In case of an important volumetric reduction (> 50%) and absence of cavity distortion, patients can be advised to try to get pregnant naturally, or, if necessary, to contact a fertility centre. There are still little data in the literature regarding pregnancies after therapy with UPA, but they are encouraging, showing good pregnancy outcome even without surgery. If this clinical program is adopted, patients should be advised to try to get pregnant or initiate ovarian stimulation after the second menstruation occurred after the end of the treatment.[48]

In the case of a good volumetric reduction of the fibroid (≥25% but <50%), but not good enough to correct the cavity distortion or make the fibroid size clinically insignificant, surgery can be an option, at this point, it should be less invasive and with less complications.

If the patient does not respond to UPA, a pre-surgical treatment with GnRH analogues can be suggested, or myomectomy.[49]

<u>2. Women not currently interested in having children</u>

Prolonged and intermittent medical treatment with UPA (4 cycles of three months, possibly repeated in case of symptom recurrence) is a good option for fertile women suffering from fibromatosis not currently interested in having children, it reaches a good control of bleeding in more than 90% of patients and regression of lesions, ≥25% in 80% of patients.[11]

Given the high recurrence rate after myomectomy, equal to 60% in 4-5 years, medical therapy can help in symptom control and to avoid, or even postpone surgery until the patient wants to try to get pregnant.[50]

Recommendation	Evidence level	Strength of recommendation
As for women with type 2 fibroids who want to try to get pregnant, treatment with UPA may be suggested, in order to reduce the size of the lesion before hysteroscopic myomectomy, or as an exclusive treatment.	II	B
If the patient does not respond to UPA, pre-surgical treatment with GnRH analogues or myomectomy can be considered.	II	B
Prolonged and intermittent medical treatment with UPA (4 cycles of three months, possibly repeated in case of recurrence of symptoms) is a good option for fertile women suffering from fibromatosis not currently interested in having children.	II	A
Given the high recurrence rate after myomectomy, equal to 60% in 4-5 years, medical therapy can help to control the symptoms and to avoid, or even postpone surgery until the patient wants to try to get pregnant.	III	B

✓ **What is the medical treatment for women in perimenopause with symptomatic type 2 to 5 uterine fibroids?**

In this situation, medical treatment should aim to induce menopause without surgery.

The use of UPA at a dose of 5 mg for four cycles of three months shows a progressive increase of both effects the volumetric reduction and the bleeding decrease. Moreover, the medium PBAC score in the period between one cycle and the one other decrease if treatment cycles are repeated.

Patients should be re-evaluated after four cycles and therapy should be re-proposed in case of recurrence of symptoms. No cases of endometrial hyperplasia were recorded in women undergoing eight-month cycles of UPA 5 mg.[10,13,14,48,51]

Recommendation	Evidence level	Strength of recommendation
Medical treatment aim to induce menopause without surgery.	I	A
The first choice treatment is UPA for four cycles of three months.	I	A

✓ **What is the medical treatment for infertile women with symptomatic type 2 to 5 uterine fibroids?**

In the case of patients with multiple fibroids, differently located, and who want to have children, medical therapy is now considered as the first-choice approach.

The efficacy of UPA, used according to an intermittent scheme which includes 2 cycles of treatment at a dose of 5 mg/day for three months alternating with two menstrual cycles has been demonstrated.[10,13,46]

In patients in wich there is a significant reduction in the volume of the fibroid (> 50%) with relief of symptoms, correction of anaemia and restoration of the endometrial cavity, surgery is not required and patients can try to get pregnant naturally. If the reduction in fibroid volume is > 25% but <50%, patients can still try to get pregnant naturally or opt for IVF.[48,52]

Medical therapy with one or two cycles of SPRMs could be an option even for patients with type 2 to 5 fibroids, with no symptoms, prior to start any in vitro fertilization or oocyte donation procedures already planned for any cause.[53]

Further clinical studies on the use of UPA in patients that are candidates for IVF are required.

However, in some cases, if the uterine cavity remains distorted or if the fibroid remains voluminous and the patient continues to be symptomatic, an indication for surgery remains.

In this case, a medical pre-treatment can allow surgery with a less invasive approach (laparoscopic myomectomy).

Despite the fact that several studies have suggested that intramural fibroids have a negative effect on fertility outcomes, it has been shown by different reviews that these results are not consistent.[54-55]

According to a meta-analysis and a review of 19 observational studies, reduced fertility is not only associated with submucous and intramural fibroids, distorting the uterine cavity, but also with the presence of fibroids that do not alter the uterine cavity.[56]

In case of symptomatic fibroids not responsive to medical therapy, myomectomy seems to be clearly indicated.

In terms of infertility, several uncontrolled studies have suggested that myomectomy produces a decrease in the rate of miscarriage in women with fibroids causing distortion of the uterine cavity.[57-58]

In a review of prospective and retrospective studies, Donnez and Jadoul reported a 49% pregnancy rate in patients who had undergone laparoscopic myomectomy.[59]

In another review, the postoperative pregnancy rate was 57%.[60] These post-myomectomy pregnancy rates have been confirmed by other studies, but the lack of randomized trials represents a major drawback.[61]

Recommendation	Evidence level	Strength of recommendation
Medical treatment is considered as the first choice approach for these patients.	III	C
There are no significant differences in pregnancy rates or obstetric or perinatal outcomes between abdominal myomectomy and laparoscopic myomectomy.	II	B

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SECTION 3: SURGICAL TREATMENTS

3.1 Hysteroscopy Surgery

3.1.1 When hysteroscopic myomectomy is the "gold standard" for the treatment of uterine fibroids?

Currently, conservative and less invasive techniques, such as hysteroscopy, are valid surgical alternatives to traditional techniques such as hysterectomy and myomectomy (laparotomy), for the treatment of symptomatic submucous fibroids.

Hysteroscopic myomectomy is the best therapeutic option for the treatment of submucous fibroids since it allows to improve the clinical conditions and to preserve the integrity of the uterine wall.

Moreover, hysteroscopic resection, compared to traditional techniques, is associated with shorter operative times, less blood loss and a lower risk of infections and adhesions. Other advantages of this technique include the reduction of surgery costs and, more importantly, a reduction in the duration of recovery and the relevant costs. Patients, in witch only myomectomy is necessary, will have a less traumatic postoperative course also in a psychological point of view.

The choice of the technique mostly depends on the intramural extension of the fibroid, as well as on personal experience and available equipment. It is well established that fibroids, completely (G0) or mostly (G1) intracavitary, can be easily removed in a single procedure with fibroid size representing the main limiting factor (generally no more than 5 cm). *"Resectoscopic slicing"* still represents the *"gold standard"* technique for the treatment of such fibroids, even if several other effective techniques including *morcellation, and office myomectomy* have been proposed, mostly for small myomas.

On the other hand, the resection of fibroids with prevalent intramural extension (G2) is advisable only for expert surgeons as it is technically hard and has a higher risk of complications respect to other hysteroscopic procedures. Currently there is still not a single technique proven to be unequivocally superior for the treatment of such fibroids. Most techniques aim to transform an intramural fibroid to a totally intracavitary lesion, thus avoiding a deep cut into the myometrium. At present, the *"cold loop"* technique developed by Dr. Ivan Mazzon seems to represent the best option as it allows a safe and complete removal of such fibroids in just one surgical procedure, while respecting the surrounding healthy myometrium. Hysteroscopic myomectomy is the ideal approach for the treatment of submucous fibroids, both for those entirely located within the uterine cavity (G0) and for those with more than 50% of their

volume in the uterine cavity (G1). Fibroids with an intracavitary component of less than 50% (G2) are harder to treat by hysteroscopy and may require long operative times. Moreover, although fibroids larger than 5 cm and with a more remarkable intramural component can be treated hysteroscopically, usually hysteroscopic myomectomy is recommended only for fibroids smaller than 5 cm in diameter.

Recommendation	Evidence level	Strength of recommendation
Hysteroscopic myomectomy is a safe and effective technique for the control of menstrual disorders and is the ideal approach to the treatment of symptomatic G0 and G1 sub-mucous fibroids, with a diameter of less than 5 cm.	III	B
Patients undergoing hysteroscopic myomectomy, especially in cases of intramural fibroids, should be informed of the risk of persistence and/or recurrence of symptoms and, therefore, of the possibility to undergo again the treatment.	III	A
Hysteroscopic myomectomy may also be recommended for symptomatic G2 sub-mucous fibroids smaller than 5cm, when performed by an experienced operator.	III	C

3.1.2 What are the indications for and the limits of hysteroscopic myomectomy in an outpatient setting?

In recent years, many uncontrolled clinical trials have been published, demonstrating the feasibility, tolerability and safety of office hysteroscopy. Already in 2002, Bettocchi assessed the efficacy, safety and acceptability of operative hysteroscopy in an outpatient setting without analgesia or anaesthesia for the treatment of benign intracavitary diseases with 5Fr bipolar electrodes.[26]

The literature available from 1990 to 2002 has clearly demonstrated that this technique allows to treat small fibroids safely, without dilatation of the cervical canal and without anaesthesia.

Fibroid treatment depends mainly on location, size and number of fibroids. Currently, it is (or should be) widely accepted that a 0.5 cm lesion affecting the uterine cavity can cause more serious damage than a 3cm lesion that develops in the serosa.

Small fibroids, whether completely (G0) or partially (G1) intracavitary, symptomatic or asymptomatic, with a size ranging from 1.5 to 2 cm, can be effectively and safely removed by ambulatory surgery using the technique described by Bettocchi.[26] It is very important to carefully evaluate the size of the lesion; since fibroids usually have a roundish shape, the linear growth in the diameter of a fibroid corresponds to the quadratic growth in its surface and to the cubed growth of its volume.

Data provided by the international literature concerning the need to treat small submucous fibroids, confirm that, for fertile women with small submucous fibroids, waiting is no longer acceptable, even if such lesions are asymptomatic, especially if they can be easily and safely removed by ambulatory surgery, with minimal patient discomfort.[26-32]

Recommendation	Evidence level	Strength of recommendation
In the case of fertile women with small and asymptomatic sub-mucous fibroids smaller than 1.5 to 2cm, waiting is not recommended.	VI	B
G0 and G1 uterine fibroids smaller than 1.5 to 2cm, whether symptomatic or asymptomatic, can be effectively and safely removed by ambulatory surgery.	V	B

3.1.3 Does hysteroscopic myomectomy result in an improvement in reproductive outcomes in infertile women?

Although epidemiological data show that most of women with fibroids are fertile, much evidence suggests that fibroids may interfere with fertility; in particular, submucous fibroids seem to exert the majority of the negative effects on reproductive outcomes. Although this association is not supported by a clear biological rationale, several hypotheses have been proposed in order to explain how submucous fibroids can cause prolonged sterility or repeated miscarriages. Fibroids may interfere with sperm migration, oocyte transport or embryo implantation. All of these effects could be mediated or altered by the contour of the uterine cavity, with a consequent increase in mechanical pressure, or by the occurrence of abnormalities in uterine contractility. Currently, however, none of these hypotheses seems to be supported by certain clinical data. Fibroids have also been associated with implant failure or premature termination of pregnancy due to focal vascular disorders of the endometrium, endometrial inflammation, secretion of vasoactive substances or a local increase in androgens.

The presence of submucous fibroids may also be associated with an increased risk of obstetric

complications (miscarriage, preterm birth, abnormal fetal presentation, placenta previa, abruptio placentae). In 2008, Klatsky reported an increase in the risk of miscarriage and preterm birth of 16% and an abnormal fetal presentation rate of 13% (about 2.5 times higher than the general population) in women with uterine fibroids compared to women with no fibroids.[32] In the same study, Klatsky also reported a twice-higher risk of placenta previa and 3% abruptio placentae in women with intramural submucous fibroids, compared to the control group.[33]

Similarly, Pritts, in his meta-analysis, confirmed the results of previous studies, including women undergoing assisted reproduction techniques.

The different studies provided by the literature are characterised by a real discrepancy in the estimated risk of adverse obstetric events in women with submucous fibroids, even if most of them show a risk twice more high respect to the general population.[33-47]

Many authors have evaluated the effects of hysteroscopic myomectomy on reproductive outcomes in infertile women. The post-operative pregnancy rate ranges from 16.7% to 76.9% with an average of 45%. This great variability can be due to the hard control of multiple concomitant factors potentially determining the condition of infertility, such as differences in the sample size, duration of follow-up, different characteristics of the patients enrolled (age, primary or secondary infertility) and to the different characteristics of the treated fibroid (number, size, intramural extension and concomitant presence of intramural fibroids). A recent cohort study showed that, in women with recurrent miscarriage and intracavitary uterine fibroids, hysteroscopic myomectomy – by restoring the normal uterine morphology – significantly improves reproductive outcomes, doubling the rate of live births. Dietterich and colleagues, on the other hand, have shown that small fibroids, which do not modify the morphology of the uterine cavity, do not seem to influence fertility, even in older women. One RCT (Boostel et al 2010) compared hysteroscopic myomectomy with the decision to not perform the surgery in 94 patients with primary infertility and the results were not statistically significant.

In general, uncontrolled studies have suggested a decrease in the rate of miscarriage after myomectomy, compared to the miscarriage rate before surgery. In a study that included women with recurrent miscarriage and/or uterine cavity distortion, who underwent myomectomy, a decrease in miscarriage rates from 21.7% to 0% in the second trimester in subsequent pregnancies was demonstrated. Other studies have also shown a remarkable decrease in the rate of miscarriage (from 61.6% to 26.3%) after hysteroscopic treatment of uterine fibroids.

Published data suggest that pregnancy, live births and miscarriage rates will normalize after myomectomy for submucous fibroids, compared to infertile women without fibroids.

In 2012, Metwallt published a review of randomized trials, about the effect of surgical treatment of fibroids on fertility, in this review he identified a study, which showed no evidence of a significant effect on the rate of miscarriage. This study also showed an increase in the spontaneous pregnancy rate after surgical treatment of submucous fibroids, while the pregnancy rate after the removal of intramural or subserosal fibroids was not increased compared to the control group (patients who had not yet undergone surgery).[48-54]

There are no randomized trials published after 2012 on this subject.

In conclusion, clinical experience and observational studies suggest that treatment of uterine fibroids could improve reproductive outcomes. However, due to the lack of large randomized clinical trials and the collection of limited and inconclusive data, it is not possible to draw conclusions on the actual effect of hysteroscopic myomectomy on fertility.

Surgical treatment of uterine fibroids is also associated with complications, including intrauterine adhesion. So, the potential benefit that could result from surgical treatment can be reversed by the negative effects of surgery on uterine integrity.

We can say, therefore, that fertility problems remain a sensitive and controversial topic, for which every treatment option must be widely discussed with the couple.

However, in women with unexplained infertility, or with a history of recurrent miscarriage or early loss of pregnancy, the removal of these lesions should always be recommended. The treatment of subserosal fibroids, on the other hand, is not recommended.

Recommendation	Evidence level	Strength of recommendation
Hysteroscopic treatment of sub-mucous uterine fibroids in women with unexplained infertility, or with a history of recurrent miscarriage is recommended, as it may improve reproductive outcomes.	II	B

3.1.4 Can the removal of asymptomatic fibroids be indicated in cases of uterine cavity distortion or in ART candidate patients, in the absence of other causes of infertility?

The development of ART (Assisted Reproductive Technology), and in particular in vitro fertilization (IVF) have helped to clarify the relationship between uterine fibroids and embryo reproductive outcomes. However, there is no consensus on the hypothesis that the presence of fibroids negatively affects post-ART reproductive outcomes and therefore on the fact that they must always be removed before ART. The position and size of the fibroid are considered key factors of post-ART reproductive outcomes.

The effect of hysteroscopic myomectomy on post-IVF reproductive outcome has not been well investigated in the literature. Among the few studies available, four meta-analyses evaluated the impact of fibroids on IVF cycles. Pritts reported significantly lower pregnancy rates and implantation rates in patients with submucous fibroids and abnormal uterine cavities, compared to the control group of infertile women without fibroids, while not showing an increase in the pregnancy rate in infertile patients undergoing surgery for intramural fibroids.

The results provided by Donnez and Jadoul confirmed that only submucous fibroids have a negative impact on embryo implantation.[55] Somigliana carried out an updated meta-analysis and reported significantly lower pregnancy rates for patients with submucosal and intramural fibroids.[55] Of the three studies assessing the impact of prior myomectomy on IVF cycles, only two included patients who underwent surgery for submucosal fibroids. A meta-analysis of these two studies shows that hysteroscopic myomectomy seems to positively affect the probability of post-IVF pregnancy. However, this positive effect could be challenged, since this meta-analysis is based on only two retrospective studies, both characterized by low sample size.[55-60]

In the international literature, there are not prospective studies comparing the removal of submucous fibroids in women undergoing ART, with a diameter of less than 1.5 cm, with no surgery (waiting behaviour).

However, even considering the potential risk of failure, we believe that patients with unexplained infertility or with a history of recurrent miscarriage should undergo surgical treatments to improve the morphology and function of the uterine cavity before undergoing any fertility treatment cycle.

Recommendation	Evidence level	Strength of recommendation
Hysteroscopic treatment of asymptomatic sub-mucous uterine fibroids in infertile women who are candidates for ART may be considered, as it may improve reproductive outcomes.	II	B

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3.2 Laparascopy

3.2.1 Laparoscopic myomectomy

The size and location of the fibroid are the main criteria for the choice of laparoscopic myomectomy.

Laparoscopic myomectomy, compared to laparotomy, offers many advantages, such as a reduction in intraoperative and post-operative morbidity, a faster recovery and good overlapping results in terms of fertility.[1-3] This procedure, however, is associated with objective difficulties, especially those related to the hysterotomic suture.

The presence of an intramural fibroid larger than 10 cm, or the presence of multiple fibroids located in different areas of the uterus, that would require numerous incisions, are generic contraindications, depending mostly on the experience of the surgeon and on the surgical technique.[4-5] Whether very long operative times are expected due to the size, location or number of fibroids, laparotomy is a more appropriate choice.

The risk of uterine rupture during pregnancy after laparoscopic myomectomy does not appear to be greater than laparotomy, in large series it was less than 1% if the hysterotomy has been adequately repaired.[6] Moderate use of electrosurgery and multilayer suture can reduce the risk of dehiscence in pregnancy.[7]

The use of morcellators is often required for laparoscopic myomectomy. It seems that 1 fibroid out of 400 is a leiomyosarcoma, as confirmed by the final histological examination, and the use of morcellators, in this case, significantly compromises the prognosis, this is why the FDA, in 2014, has discouraged the use of these devices.[8] Therefore, the use of morcellators is not recommended in case of suspected malignancy. Endobag morcellation, on the other hand, is an innovative technique not associated with oncological risks. To perform this technique, the removed mass must be placed inside a laparoscopic endobag, whose edges are pulled out by one of the surgical incisions to allow a safe manual or automatic morcellation and to avoid nebulization of cells in the peritoneal cavity. This is a technique similar to that used routinely to extract adnexal masses to avoid spillage, which would change the stage of disease in case of malignancy.[9]

Today new endobags are available on the market, which allow the insertion of trocars inside them to facilitate the procedure of morcellation.[10-11]

Generally, the use of GnRH analogues is not recommended as it does not reduce operative times and may alter the anatomical limits of the fibroid, and seems to be associated with a higher rate of reoccurrence, but has proved useful in patients with low levels of preoperative hemoglobin.[12]

A 2016 retrospective study shows that a pre-treatment with UPA three months before performing a laparoscopic myomectomy

is strongly recommended for patients with voluminous uterine fibroids, since operative times are reduced, as well as intraoperative blood loss, and, consequently post-operative blood transfusions.[13]

Recommendation	Evidence level	Strength of recommendation
Laparoscopic myomectomy, compared to laparotomy, where feasible, is associated with less postoperative morbidity but with overlapping results in terms of fertility.	I	A
Contraindications for a laparoscopic myomectomy include the presence of intramural fibroids larger than 10 cm or the presence of multiple fibroids located in different areas of the uterus that would require numerous incisions.	V	C
Multilayer sutures are recommended rather than single-layer sutures.	II	B
The use of morcellators is to be considered only when there is a low risk of malignancy and after discussing the potential risks with the patient.	III	B

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3.3 Hysterectomy

Hysterectomy has long been considered as the first-choice treatment for patients with large fibroids resistant to medical treatment and symptomatic fibroids in women who are not trying to get pregnant or are near to menopause.In recent years, laparoscopy has become the most used technique, compared to laparotomy, even if, according to recent data provided by Cochrane, the vaginal approach is still recommended under certain conditions.[1-2]

Contraindications for laparoscopic hysterectomy include a uterine volume equal to pregnancy at 13-14 weeks.

Recommendation	Evidence level	Strength of recommendation
Hysterectomy is the first choice approach for symptomatic uterine fibroids resistant to medical therapy in women who are close to menopause, and, in any case, at the end of the reproductive process.	I	A

1) Donnez O, Jadoul P, Squifflet J, Donnez J. ***A series of 3190 laparoscopic hysterectomies for benign disease from 1990 to 2006: evaluation of complications compared with vaginal and abdominal procedures****. BJOG 2009;116:492–500.*

2) Aarts JW, Nieboer TE, Johnson N, Tavender E, Garry R, Mol BW, Kluivers KB. ***Surgical approach to hysterectomy for benign gynaecological disease****. Cochrane Database Syst Rev 2015; 8:CD003677.*

3.4 Laparotomy

The traditional laparotomy surgical technique is still the most used in our country today. The number of fibroids (>3), their size (> 7 cm), as well as their location, often associated with higher risks (intramural fibroids near the ostia or some intraligamentary fibroids that come in contact with big vessels and/or the ureters) are the main criteria for the choice of the traditional technique. Laparotomy is the most invasive surgery for patients, with a higher rate of postoperative complications than minimally invasive techniques and with longer hospitalization and recovery times.[1]

3.4.1 What are the advantages of minilaparotomy?

Minilaparotomy (transverse suprapubic skin incision < 9 cm) is a valid alternative to laparoscopic myomectomy, especially for those operators who are not familiar with laparoscopic sutures.[2] According to a randomized clinical trial and a non-randomized trial, it offers better aesthetic results, compared to a classical laparotomy, with reduced postoperative pain, less blood loss and faster postoperative recovery times.[3-4]

Laparoscopically assisted minilaparotomy is a technique often used to avoid morcellation, and has been proven to be better than classical minilaparotomy in terms of intraoperative and postoperative outcomes in a randomized clinical trial conducted in China.[5]

The limits of minilaparotomy reported in the literature include the position of the fibroid in the isthmic and posterior region, fibroid size (> 12cm), patients' obesity (BMI> 27), intralegamentary fibroids and to concomitant adnexal pathologies not previously diagnosed.[6-7]

Recommendation	Evidence level	Strength of recommendation
Minilaparotomy offers some advantages compared to classical laparotomy and may, in some cases, be a valid alternative to laparoscopy.	II	B

1) Jin C, Hu Y, Chen XC, Zheng FY, Lin F, Zhou K, Chen FD, Gu HZ. **Laparoscopic versus open myomectomy--a meta-analysis of randomized controlled trials**. Eur J Obstet Gynecol Reprod Biol. 2009 Jul;145(1):14-21.
2) Glasser MH. **Minilaparotomy myomectomy: a minimally invasive alternative for the large fibroid uterus**. J Minim Invasive Gynecol. 2005 May-Jun;12(3):275-83.
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5) Tan J, Sun Y, Zhong B, Dai H, Wang D. **A randomized, controlled study comparing minilaparotomy versus isobaric gasless laparoscopic assisted minilaparotomy myomectomy for removal of large uterine myomas: short-term outcomes**. Eur J Obstet Gynecol Reprod Biol. 2009 Jul;145(1):104-8.
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7) Parker WH. **Uterine myomas: management**. Fertil Steril. 2007 Aug;88(2):255-71.

✓ <u>*Does preoperative pharmacological treatment improve the surgical prognosis?*</u>

The main purpose of preoperative medical treatment of uterine fibroids is to obtain a reduction of intraoperative blood loss, as well as a reduction in the volume of the fibroids. However, many studies have shown greater difficulties in the removal of fibroids after medical therapy due to the frequent colliquation of the fibroid tissue, mainly linked to the use of GnRH analogues.

GnRH analogues and, recently, also SPRMs are the most frequently used medications.

1) Baranowski W. ***Ulipristal acetate before high complexity endoscopic (hysteroscopic, laparoscopic) myomectomy - a mini-review****. Prz*

Menopauzalny. 2016.
2) Ferrero S et al. ***Three-month treatment with ulipristal acetate prior to laparoscopic myomectomy of large uterine myomas: a retrospective study****. Eur J Obstet Gynecol Reprod Biol. 2016.*
3) Chang WC e al. ***Comparison of Laparoscopic Myomectomy in Large Myomas With and Without Leuprolide Acetate****. J Minim Invasive Gynecol. 2015.*
4) Lethaby A et al. ***Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids.*** *Cochrane Database Syst Rev. 2001.*
5) Ferrero S et al. ***Ulipristal Acetate Before High Complexity Hysteroscopic Myomectomy: A Retrospective Comparative Study.*** *J Minim Invasive Gynecol. 2016.*

✓ *Is prevention of post-surgical adhesions a valid reason for choosing laparoscopic myomectomy?*

The development of adhesions in gynecological surgeries is particularly relevant, because of its potential impact on the reproductive function. For women who want to get pregnant, laparoscopy, if performed by expert hands and qualified operators, should be preferred, also because it is associated with a reduced risk to develop adhesions compared to laparotomy.

1) Asgari Z et al. ***Intrauterine synechiae after myomectomy; laparotomy versus laparoscopy: Non-randomized interventional trial****. Iran J Reprod Med. 2015.*
2) Gambadauro P et al. ***Intrauterine Adhesions following Conservative Treatment of Uterine Fibroids****. Obstet Gynecol Int. 2012.*
3) Campo S et al. ***Reproductive outcome before and after laparoscopic or abdominal myomectomy for subserous or intramural myomas****. Eur J Obstet Gynecol Reprod Biol. 2003.*
4) Metwally M et al. ***Surgical treatment of fibroids for subfertility****. Cochrane Database Syst Rev. 2012.*
5) Gutt CN et al. ***Fewer adhesions induced by laparoscopic surgery?*** *Surg Endosc. 2004.*

SECTION 4: ALTERNATIVE TREATMENTS

Uterine Artery Embolization (UAE), thermal ablation and uterine artery occlusion are all alternative procedures.

4.1 Uterine Artery Embolization

UAE is practiced by interventional radiologists injecting an embolization agent into the uterine arteries with the aim of reducing symptoms associated with fibroids. Although UAE is highly effective in the treatment of symptoms (reduction of bleeding and decrease in the size of the fibroid), the risk of a second surgery is high: 15 to 20% after successful embolization, and greater than 50% in cases of incomplete embolization. The impact of UAE on the ovarian reserve and reproductive outcomes are an unresolved theme.[1] A systematic review of 15 randomized trials and prospective cohort studies showed that loss of ovarian function occurred mainly in women older than 45 years.[2] A randomized clinical trial that compared this procedure to myomectomy showed a lower rate of pregnancies and a higher incidence of miscarriages in patients treated with UAE.[3]

Results and complications of UAE were assessed in a very recent review, which pointed out that the desire of a future pregnancy remains a relative contraindication, as the lack of data in the literature does not guarantee a successful pregnancy outcome.[4]

A meta-analysis of 2013 showed that the complication rate after UAE is lower than surgical procedures, but the risk of a second surgery is higher.[5]

4.2 Thermal ablation

Magnetic resonance-guided focused ultrasound (MRgFUS) surgery is a type of thermal ablation that uses MRI to visualize fibroids and to define their edges. Focused ultrasound treatments exploit the direct energy of acoustic waves at a specific point within the fibroid to induce a temperature increase with thermal coagulation and necrosis of the leiomyomatous tissue.

Damage to the surrounding tissue should be minimal, but, the impact on adjacent critical structures cannot be ruled out.[6] Case-series showed in the literature demonstrate an adequate short-term efficacy and a complication rate of about 7%, but these are mostly minor complications, such as small skin burns and post-procedure pain, while intestinal perforations have been rarely reported.[7-9]

A recent randomized placebo-control study

showed that in women who undergo this treatment there may be a placebo effect to explain the improvement in symptoms.[10]

The results in terms of pregnancies in some of these cases are limited but encouraging.[11]

The main limitations to the use of this technique are the selection of patients that may undergo this procedure, long sessions, the possibility to treat only a single fibroid per session and the relevant costs, which are still very high.[12]

Other fibroid thermal ablation systems include laser, cryotherapy and radiofrequency ablation.

Fibroid laser ablation uses MRI-guided endoscopic or percutaneous methods. A low-power laser (wavelength: 1,064nm) is used, which penetrates deeply into the tissue inducing a laser-photocoagulation of the fibroid cells. A substantial shrinkage of the fibroid (50-70%) can be achieved, but there is still no strong evidence in the literature.[13-15]

Cryotherapy uses argon gas to quickly freeze and unfreeze the fibroid. It can be performed by endoscopy or, since 2000, as an MRI-guided technique.[16-17]

Radiofrequency ablation has a broader range compared to cryotherapy (about 6cm) in a 30-minute session, but is not compatible with magnetic resonance, and is performed using double laparoscopic and ultrasound or CT guidance. The reduction in the volume of fibroids is associated with an improvement in symptoms.[18-20]

4.3 Uterine artery occlusion

Uterine artery occlusions are performed with the laparoscopic, laparotomic or vaginal approach with locking devices that remains in place for 6 hours, determining the fibroid ischemia, interfering with the blood supply of the uterus.[21] However, this technique is not recommended for women who want to get pregnant in the future.

Recommendation	Evidence level	Strength of recommendation
UAE is effective for symptom control, but there is a high risk of undergoing another procedure and a lower rate of pregnancies compared to myomectomy.	II	B
The results of thermal ablation techniques are encouraging, but there are no data on long-term results.	III	C

1) Gupta JK, Sinha A, Lumsden MA, Hickey M. **Uterine artery embolization for symptomatic uterine fibroids**. Cochrane Database Syst Rev. 2014;12:CD00507.
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MRI guidance for the treatment of fibroids. Curr Opin Obstet Gynecol. 2000;12(4):277–282.
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17) Cowan BD. **Myomectomy and MRI-directed cryotherapy**. Semin Reprod Med. 2004;22(2):143–148.
18) Milic A, Asch MR, Hawrylyshyn PA, et al. **Laparoscopic ultrasound-guided radiofrequency ablation of uterine fibroids**. Cardiovasc Intervent Radiol. 2006;29(4):694–698.
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