Uterine Fibroids Management In Asymptomatic Women

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Abstract: Uterine myomas or fibroids represent the most common pathology in female genital tract. There are marked differences by race in both prevalence and incidence. Pathogenesis of fibroids is still unclear. Several risk factors have been identified, ranging from genetic predisposition to variable lifestyles, with recurrence in positive family history for fibroids. Although most of them are asymptomatic, they may cause abnormal uterine bleeding and pelvic pain, and are associated with several pregnancy-related complications, spontaneous abortion, preterm delivery, and cesarean delivery. Moreover, fibroids are associated with several adverse reproductive outcomes and in 10% of infertility case. These fibroids related problems can negatively impact daily living and quality of life. Frequently, the diagnosis is incidental and the treatment is based on symptoms and patient' wishes, depending on age, numbers and fibroid' size, woman's fertility plans and risk of malignancy. Because of the high estimated prevalence and costs associated with treatments, the direct and indirect costs of uterine fibroids are substantial. This manuscript reviews the current literature on uterine fibroids, focusing on updated researches on fibroid management in asymptomatic women. Unfortunately, from the data examined, there is no univocity of diagnosis and treatment, thus, further large studies are need to define the management of asymptomatic fibroids.

Keywords: Uterine fibroids, Myoma, Leiomyosarcoma, Reproductive outcomes, Infertility, pregnancy-related complications, Spontaneous abortion, Preterm delivery, Cesarean delivery.

INTRODUCTION

Uterine fibroids represent the most common pathology in female genital tract. Although most of them are asymptomatic, they may cause abnormal uterine bleeding and pelvic pain. There are few data about real incidence of fibroids, because 40-60% of them are asymptomatic and are found incidentally in course of routine gynecological examination, pelvic imaging or during other procedures [1]. Generally, fibroids are largely asymptomatic, but they can become symptomatic and, despite their relative frequency, the pathogenesis and the clinical evolution are still poorly understood. Fibroids are well circumscribed, firm, grey-white and with a whorled cut surface (Figure **1**). They may degenerate, especially in pregnancy, and become soft with a yellowish hue in necrosis or a reddish color (Figure **2**), due to hemorrhaging [2]. Nevertheless, guidelines do not clarify univocally on management and on widely accepted indications in asymptomatic patients. Here, the aim of this manuscript is to evaluate current scientific literature on management of fibroids in asymptomatic patients.

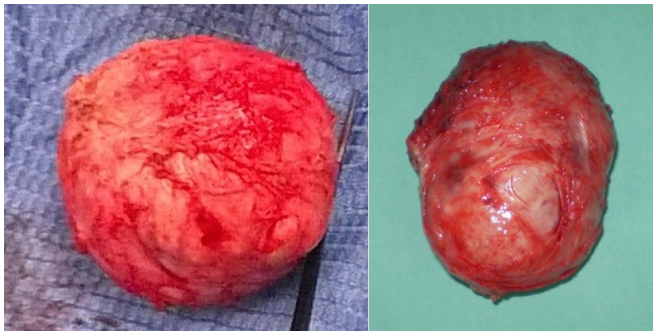

Figure 1: Fibroids are well circumscribed, firm, grey-white and with a whorled cut surface.

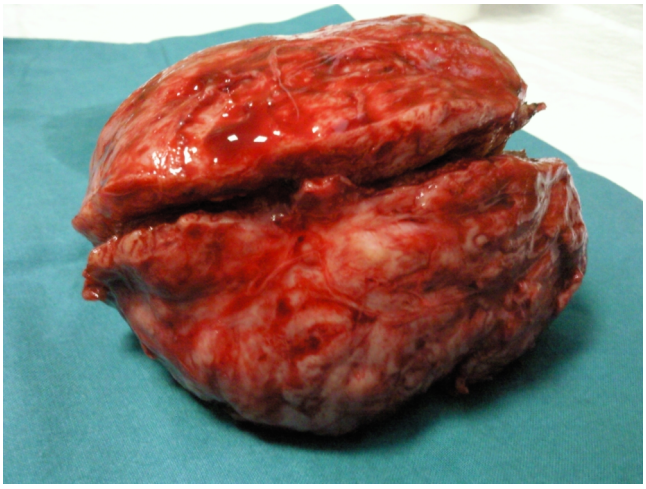

Figure 2: Fibroid in pregnancy removed during cesarean section.

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E-ISSN: 2408-9761/19

METHODS

This review was conducted examining more common scientific database, as PubMed (MEDLINE), Web of Science databases, EMBASE, Cochrane Library and Scopus. These databases have been investigated for asymptomatic fibroids, in the last 10 years, searching papers in English-language, evaluating epidemiology, biology and management of asymptomatic fibroids. Included keywords for the search were "Uterine fibroids, myoma, leiomyosarcoma, clinical diagnosis, treatment and management". All reports were analyzed and evaluated for data. Investigations, whose full manuscript or baseline characteristics were not available and those not written in English language were excluded from this investigation. Final data were included in the manuscript.

HISTOLOGY AND BIOLOGY OF FIBROIDS

In 65-70% of cases leiomyomata are multiple and can be found in various locations most frequently within the wall of the uterus (Figure **3**) where they can expand in the myometrium (Intramural leiomyoma), beneath the endometrium (Figure **4**), simulating a polyp (submucosal leiomyoma), beneath the serosal surface (subserosal leiomyoma) (Figure **5**), within the broad ligament, simulating an adnexal neoplasia (infraligamentous leiomyoma) or at the isthmus (Figure **6**) or the myometrium of the neck (cervical leiomyoma). The compression of the endometrium causes atrophy and erosion with bleeding. Subserosal fibroids can be pedunculated (Figure **7**) and, in some cases, can separate from the uterus and create a new vascular peduncle with another nearby organ (parasitic leiomyoma) [2].

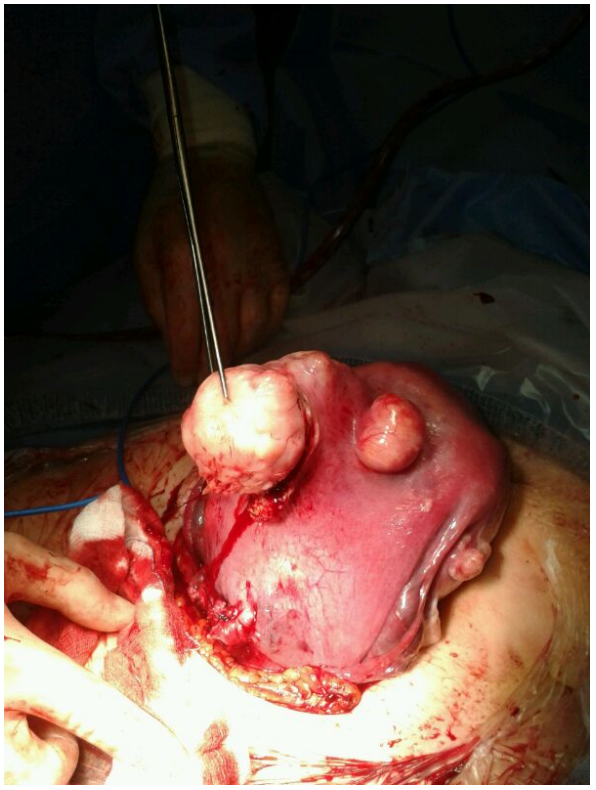

Figure 3: Laparotomic myomectomy showing many fibroids scattered in the context of the uterus.

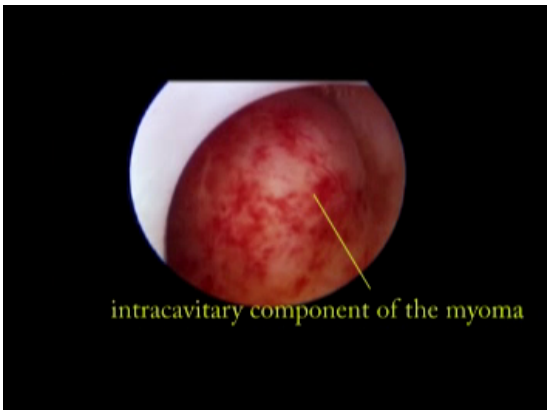

Figure 4: Hysteroscopic image of submucous G1 fibroid.

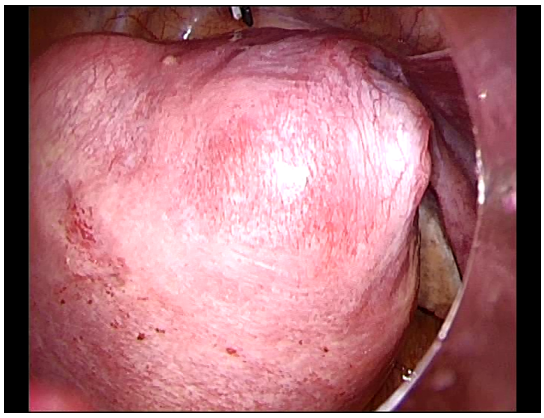

Figure 5: Subserosal fibroid.

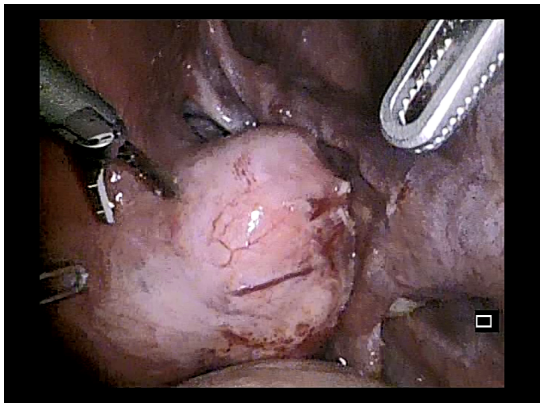

Figure 6: Isthmic fibroid.

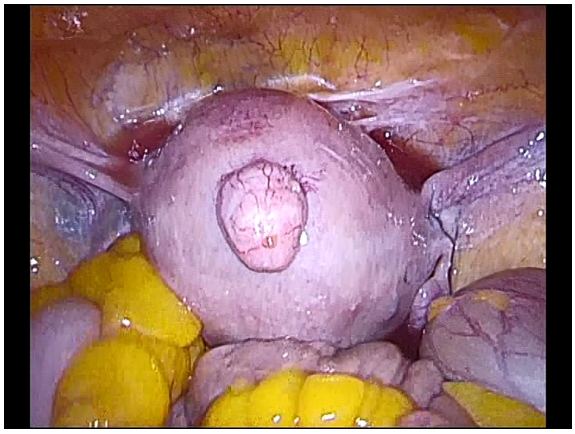

Figure 7: Pedunculated fibroid.

The fibroids' biology is still controversial and this makes the prediction of possible symptom of the fibroma very difficult. Histologically, the tumor is made up of cells similar to that of the contiguous endometrium (elongated, eosinophilic cytoplasm with central, blunt-ended, pale elongated nucleus, sometimes with clumped chromatin. The cells form whirling fascicles interlaced at right angles. This arrangement clearly distinguishes the leiomyoma from the surrounding myometrium, which shows a more regular pattern of the muscle fibers. Furthermore, a large number of tumors show a clear border with the myometrium (Figure **8**), even forming a valley, exaggerated by fixation artefact, with the formation of a ring of compressed myometrial cells [2].

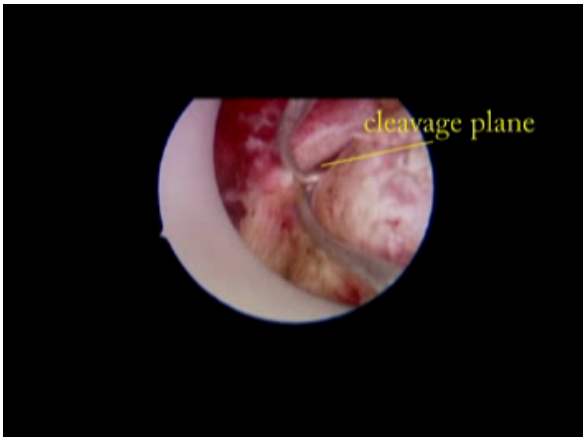

Figure 8: Hysteroscopic image that demonstrates the present space between myoma and myometrium (the cleavage plane).

Histopathological analysis revealed that they are usually surrounded by a fibro-neuro-vascular pseudocapsule (Figure **9**), as neurovascular bundle, rich of neuropeptides and neurofibers. This neurofibrovascular structure of few millimeters separates the myometrium from the fibroid (Figure **10**) and allows the enucleation of the myoma in an atraumatic manner and the subsequent activation of the muscular regeneration processes [3].

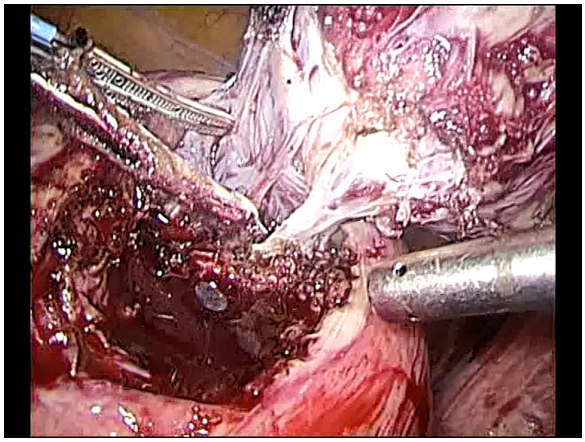

Figure 9: The laparoscopic enhancement, during myomectomy, of the fibro-neuro-vascular pseudocapsule, as a neurovascular bundle surrounding fibroid.

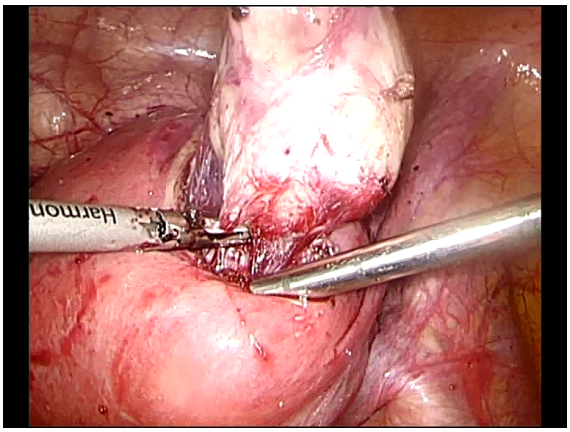

Figure 10: The pseudocapsule is neurofibrovascular structure of few millimeters separating the myometrium from the fibroid.

Fibroids' microscopic analysis revealed the presence of dense cellular bundles, with a medium mitotic activity of 0.8±0.3 mitotic figures (MF) per 10×microscopic field (10 HPF) without cellular atypia [4]. On the contrary, in case of atypical fibroids, histologic slides show cells with bizarre polylobulated and hyperchromic nuclei, with moderate/severe atypia and medium mitotic activity accounting for 1.2±0.3 MF/10 HPF [4]. The leiomyosarcoma histological analysis usually show cells with moderate/severe atypia and high mitotic activity (13.2±3.4 MF/HPF 10), with hemorrhagic and necrotic areas [4].

Generally, fibroids are sensitive to circulating estrogens, which will either cause them to grow or to

maintain their size. A study on 262 fibroids in 72 premenopausal women analyzed by magnetic resonance imaging (MRI), performed by Peddada *et al.*, tracked fibroids' growth and reporting these conclusions: 1) the median fibroids growth rate is 9% per 6 months and it declines with age ($p<0.05$);2) single fibroids shows rapid growth more than multiple fibroids ($p<0.06$), maybe for the less competition for uterine blood supply; 3) a small percentage of fibroids (7%) should demonstrate a spontaneous regression also in pre-menopausal women with regular menses (more than 20% of size in 6 months); 4) many of the shrinking fibroids show loss of arterial blood flow and necrosis (it could suggest that vascular events may be involved in shrinking, rather than hormonal changes); 5) different fibroids within the same woman present different growth rates ($p<0.001$) [5].

On the contrary, Mavrelos *et al.* [6] concluded that fibroids' size at the initial diagnosis is a significant independent predictor for subsequent fibroids growth ($p=0.01$). In this investigation [6], fibroids measuring less than 20 mm and more than 50 mm in diameter at initial US analysis show a growth rate up to three times higher than fibroids ranging 20-50 mm. Thus, Mavrelos *et al.* concluded that the fibroids' growth is unilinear: they initially start to grow quickly, then they slow down growth until the fibroid reaches a certain size, to resume a more rapid growth. This is independently from their position in the uterus [6]. The median fibroids growth rate of his study, on the contrary of the growth rates reported by Peddada *et al.* [5], was 35.2% at one year, with a spontaneous regression rate of 21.3%. In addition, Baird *et al.* [7] investigated the fibroids growth in 101 fibroids from 36 women, measured at enrolment, 3, 6, and 12 months by MRI, resulting in three interval-specific growth rates. They observed growth spurts in 37 (40%) lesions, with larger fibroids having less short-term changes than smaller one, concluding that short spurts of growth are common for fibroids, suggesting that tumor biology may change quickly.

FIBROIDS AND INFERTILITY

Fibroids are currently reported as cause of infertility; literature shows fibroid in approximately 5-10% of infertile patients and are the only cause in 1-2.4% of patients affected [8].

Different theories have been proposed to explain the effects of fibroids on fertility, but the mechanisms involved are not clear. It is generally accepted that the anatomical location of a fibroid as a submucous fibroid may impair fertility, but about the influence of intramural and subserosal fibroids in causing infertility no consensus has ever been achieved. Fibroids may distort the uterine cavity making it enlarged, elongated and altering its contour and surface area (Figure **11**). Intramural fibroids may cause dysfunctional uterine contractility (Figure **12**) which may interfere with sperm migration, ovum transport or nidation. Fibroids may also be associated with implantation failure or gestation discontinuation due to focal endometrial vascular disturbance, endometrial inflammation, secretion of vasoactive substances or an enhanced endometrial androgen environment [9].

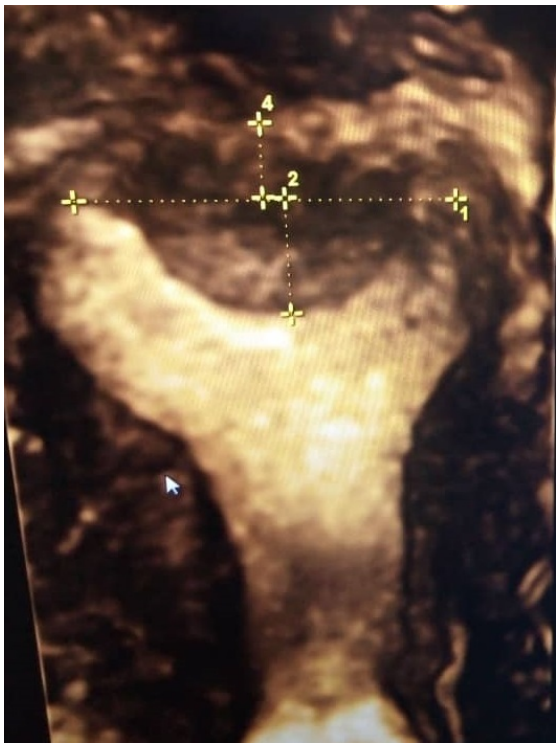

Figure 11: An ultrasonographic 3D scan showing fundal submucosal fibroids distorting the uterine cavity.

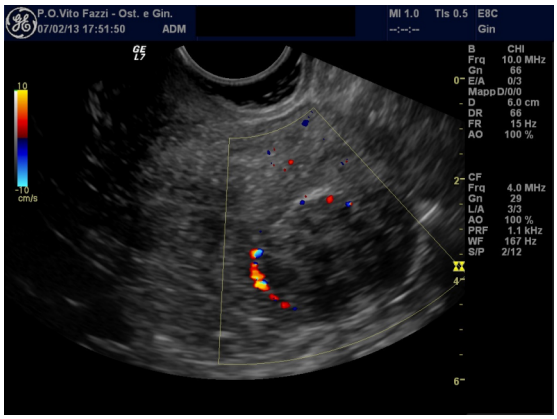

Figure 12: An ultrasonographic 3D scan showing an intramural fundal fibroid.

Pritts *et al.* investigated the impact of fibroids on fertility and of myomectomy in improving outcomes, showing that patients with submucosal fibroids have a relative risk (RR) of 0.36 of achieving clinical pregnancy, 0.28 of implantation rate and a RR of 0.32 of having a live birth when compared to controls without fibroids [10]. Basing on such data, clinicians usually advise patients to remove submucosal fibroids for prevention of subfertility, miscarriage and later pregnancy complications. On the contrary, the effect of intramural fibroids on infertility is more controversial, while subserosal (Figure **13**) and pedunculated fibroids (Figure **14**) have no impact on fertility and they are unlikely to cause adverse fertility outcomes [11].

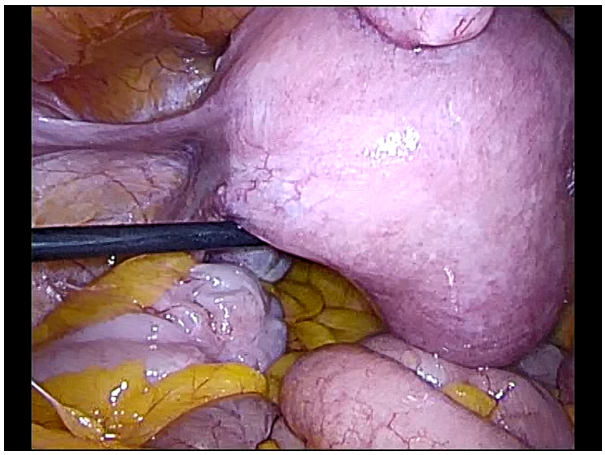

Figure 13: A laparoscopic image showing a posterior subserosal fibroid of the uterine body.

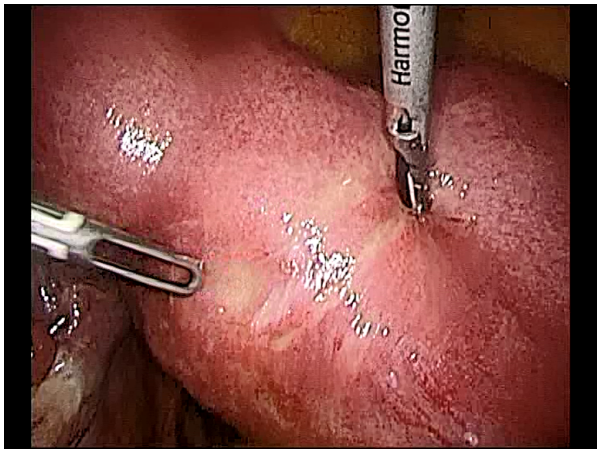

Figure 14: A laparoscopic image showing a posterior pedunculated fibroid of the uterine body.

Oliveira *et al.* [12] investigated on fertility and fibroids' size, evaluating patients with intramural fibroids: if they were greater than 4 cm, they show a significantly (p=0.025) lower pregnancy rate than those with fibroids ≤4 cm (29% vs 51 % respectively).

FIBROIDS' IMPACT ON OBSTETRICAL OUTCOMES

Fibroids in pregnancy (Figure **15**) are linked to an increased risk of obstetrical problems, as fetal mal-presentation, placenta previa (Figure **16**), premature rupture of membranes, preterm birth, miscarriage, postpartum hemorrhage, cesarean section (CS) complications. Miscarriage and preterm birth are the most commonly reported pregnancy complications in pregnants with fibroids.

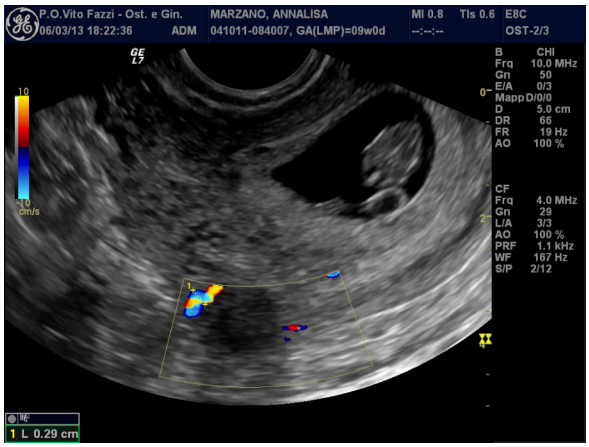

Figure 15: An ultrasonographic transvaginal scan image showing a posterior subserosal fibroid at 10 weeks of pregnancy.

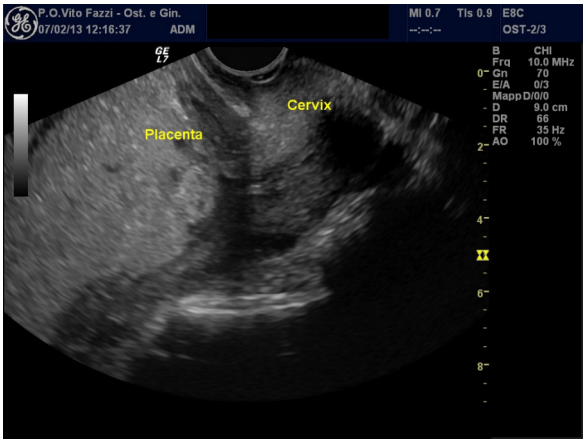

Figure 16: An ultrasonographic transvaginal scan image showing a placenta previa at 28 weeks of pregnancy.

About preterm delivery, Klatsky *et al.* [13] reported the rate of preterm delivery in these patients is 16%, whereas Lai *et al.* [14] reported, always such pregnants, an increased risk at gestational age <34 weeks (OR 1.7), <32 weeks (OR 1.9), and <28 weeks (OR 2.0). Conti *et al.* [15], in a multicenter observational retrospective study, reported 15.25% cases pregnants with fibroids VS 4% in the health cases (p<0.0001). About delivery timing, Shavel *et al.* [16] investigated patients with fibroids compared to a

control group with no fibroids or small fibroids (<5 cm) and demonstrated those with large myomas (>5 cm) delivered at a significantly earlier gestational age.

About miscarriage risk in pregnants with fibroids, Klatsky *et al.* [13] reported an increased risk of 15.3% vs 7.7% of control group (OR 1.34) for intramural fibroids and 46.7% vs 21.9% for submucosal ones (OR 3.85) [23], whereas Pritts *et al.* [10], in their meta-analysis, on 23 studies of women submitted to assisted reproductive technology (ART), confirmed that any location of a fibroid was associated with an increased risk of miscarriages (OR 1.7) versus patients without fibroids, and this two-fold increased risk was furtherly confirmed by other studies [13, 14, 17-20].

About the risk of placenta previa in pregnants with fibroids (Figure **17**), two studies reported an approximately twofold increased risk [21, 22], while the risk of abruptio placentae associated with fibroids was reported in three studies [13, 21, 22], with an estimated the frequency of placental abruption of 3.0% (115/4159) in patients with fibroids vs 0.9% in control patients (517/60,474) (p=0.001).

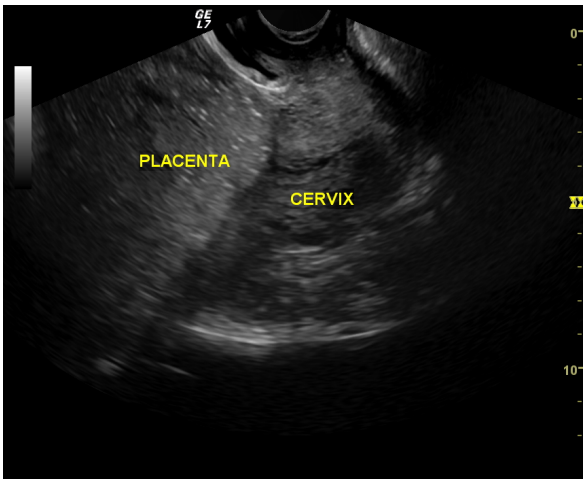

Figure 17: An ultrasonographic transvaginal scan image showing a placenta previa at 31 weeks of pregnancy.

About abnormal fetal presentation, Klatsky *et al.* [13] reported an increased rate in pregnants with fibroids, with a cumulative rate of 13% in patients with fibroids versus 4.5% in control group, whereas Stout *et al.* [17], the percentage was substantially lower, but higher than in control group, with 5.3% compared to 3.1% (p=0.01) and Navid *et al.* [22] found breech presentation in 12.5%of pregnants.

About association of fibroids and CS delivery, Klatsky *et al.* [13], reported a high percentage of CS in pregnants with fibroids, till 48.8% versus 13.3% of those without fibroids, confirmed also by Stout *et al.* [17], whose reported a CS rate of33.1% vs 24.2 1%, even after excluding diagnoses of placenta previa and breech presentation. Michels *et al.* [23] evaluated 2.635 deliveries, reporting a 27% increase risk of CS compared with those without myomas (RR, 1.27), so as reported the study of Ciavattini *et al.* [19], although the increased risk was limited to women with multiple fibroids.

About the post-partum hemorrhage, Klatsky *et al.* [13] reported a rate of 2.5% in women with fibroids and 1.4% in those without (p=0.001), whereas Conti *et al.* [15] showed a significant postpartum bleeding in 11,4% of cases versus 3,2 % of control group (p < 0.001).

FIBROIDS TREATMENT IN ASYMPTOMATIC WOMEN

Fibroids are preferentially treated by surgery, as for myomectomy; their enucleation is linked to vaginal, abdominal or hysteroscopic approach, depending on location, number and size. In infertile women, submucosal fibroids are usually managed hysteroscopically in single time (Figure **18**), if fibroid size is < 5 cm, but larger fibroids often need repeated procedures [24]. There is no univocity in agreeing on the advantage of hysteroscopic myomectomy in increasing pregnancy rate [25].

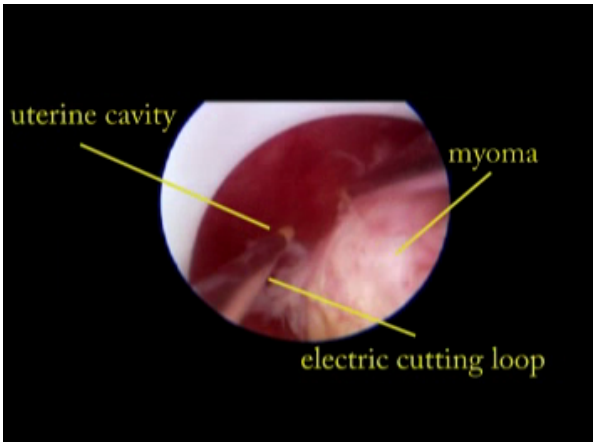

Figure 18: An hysteroscopic image showing a submucosal fibroids removal by electric cutting loop.

Patients who undergo myomectomy for submucosal fibroids have been shown to have higher clinical pregnancy rates, with a RR of 2.03 compared to women with fibroids in situ who did not undergo myomectomy (p= 0.028) [26-29].

The issue of removing intramural myomas with a positive impact on female reproduction is very controversial; reports of improved fertility following myomectomy for intramural lesions were published [30], with these conclusions: submucosal fibroids with an intracavitary component impair fertility and hysteroscopic excision could be of benefit improving pregnancy rates; removal of intramural fibroids >5 cm by laparoscopic or laparotomic myomectomy improves fertility; surgical management of subserosal fibroids is not required to restore fertility.

A recent consensus [31] on management of asymptomatic submucous fibroids in women in reproductive age, proposed the following management:

1. The use of transvaginal ultrasound to document the number, size and location of the submucous myomas; with subsequent in-office hysteroscopy considering, when feasible, a see-and-treat approach.

2. When immediate fertility is not entertained and in the presence of one or more asymptomatic submucous myomas smaller than 15 mm, hysteroscopic myomectomy is recommended but expectant management is acceptable. If expectant management is favored, clinical surveillance of symptoms and serial transvaginal pelvic ultrasound to monitor myoma's growth are recommended.

3. When immediate fertility is a priority and in the presence of one or more asymptomatic submucous myomas ≥15 mm, hysteroscopic myomectomy is recommended.

4. Among the different available hysteroscopic techniques, the cold loop resectoscopic myomectomy (Figure **19**) should be the favored approach, allowing to preserve as much healthy myometrium as possible; other hysteroscopic myomectomy techniques such as dissection, vaporization, or morcellation by Hysteroscopic Tissue Removal systems (HTRs) are acceptable. Finally, the use of 16 Fr mini-resectoscope, when available, should be considered.

5. The use of both, bipolar or monopolar energy devices for hysteroscopic myomectomy, is equally acceptable. Always keeping an accurate monitoring of the fluid balance regardless of the type of distention media used, especially in case of prolonged procedures and in patients with comorbidities with a known impact on fluid hemodynamics such as heart, lung or kidney disease.

6. The use of hysteroscopic laser energy for enucleation of submucous myomas is a promising therapeutic option, which needs further investigation.

7. Type 0 and type 1 submucous myomas are more likely to be completely removed in one-step approach; conversely, type 2 submucous myomas could require a multi-staged procedure. Moreover, the endoscopist may consider performing the Office Preparation of Partially Intramural Myomas (OPPIuM) technique, which consist of making an incision of the endometrial mucosa covering the myoma using hysteroscopic scissors or bipolar electrode, along its reflection line on the uterine wall, up to the identification of the cleavage surface between the myoma and its pseudocapsule. In case of intracavitary myomas ≤40 mm, the subsequent second-step excision can also be safely performed in office-based setting four weeks later. Conversely, for intracavitary myomas >40 mm, a second-step resectoscopic procedure is recommended.

8. Suppressive medical therapy aiming to cause endometrial hypotrophy and reduction of submucous myoma volume may be considered before hysteroscopic myomectomy for submucous myomas ≥15 mm. However, available data is insufficient to identify the best pharmacologic strategy.

9. Cervical priming is recommended to facilitate dilation before hysteroscopic myomectomy of submucous myomas larger than 15 mm, especially in nulliparous women. However, available data is insufficient to identify the best strategy to prime the cervix.

10. The use of prophylactic antibiotic administration before hysteroscopy in office setting and resectoscopic myomectomy in the operating room is not recommended, except in case of resectoscopic surgery in women with history of pelvic inflammatory disease.

11. Although the risk of intrauterine adhesion formation after resectoscopic myomectomy is low, it should be minimized by using the cold

loop enucleation technique, cognitive use of energy on pure "cut" setting minimizing thermal spread, and the use of anti-adhesion therapy.

12. A "second-look'' hysteroscopy should be performed within 3 months of a resectoscopic myomectomy to evaluate the uterine cavity and early treatment of possible intrauterine adhesion formation.

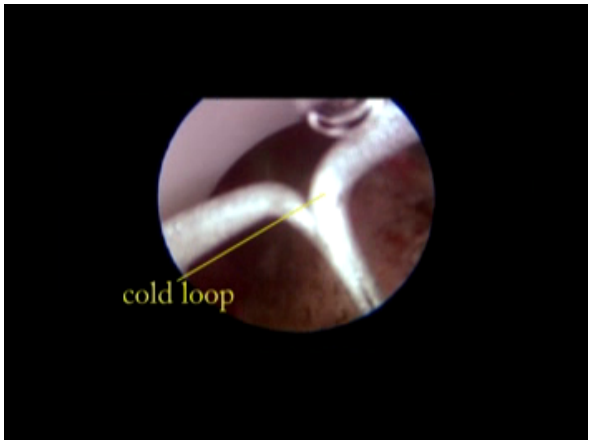

Figure 19: The cold loop resectoscopic myomectomy.

FIBROIDS AND RISK OF MALIGNANCY

Generally, fibroids do not arise from uterine myomas as a biological progression, excepting rare cellular or atypical variants, and from the data so far collected, it is unsure if fibroids have a genetic origin. In fact, it is still not well understood the biological origin of fibroids. The debate is focused on the possibility of sudden growing up of fibroids from uterine muscle cells or if there is a "sarcomatous degeneration" by a karyotypic evolution of fibroids from a benign myoma. Literature therefore stated, after a genetic consensus, that most leiomyosarcoma (LMS) arise independently [32].

The LMS is a rare aggressive tumor diagnosed usually after menopause, around 60 years of age, very aggressive and with a poor prognosis too in early-stage, due to an early hematogenous spread. The likelihood ratio of finding an LMS in a female population presenting a uterine mass is approximately 0.1 to 0.28% and it accounts for 2-5% of uterine malignancies [33].

Symptoms may be vague and include uterine bleeding, abdominal girth, pelvic pain or pressure [34]. The fast growth of intrauterine mass during one year should be considered a potential LMS, but it is not sufficient to differentiate the diagnosis from other uterine enlarging masses. The increased LMS risk was not considered in a large, since rapid growth generally is in a benign myoma and in an LMS, and no open aggressive treatment is warranted to avert the presence, "a priori", of a malignant tumor [35,36]. Postmenopausal women in estrogen replacement therapy (ERT) have either a lower risk of LMS or a small increase of myoma already present prior to ERT [37].

There are no diagnostic radiologic or ultrasonographic (US) tests, that can really distinguish benign myomas from LMS.

Besal *et al.* evaluated endometrial biopsy or curettage in LMS diagnosis [38]. They reported a sensitivity of 86% and a specificity of 67%. Currently, the diagnosis of ULMS is only by histology after a myomectomy or a hysterectomy for presumed myomas. Pelvic US is typically the routinely exam to investigate uterus with myomas. The US evaluation of a uterine mass could identify features compatible with LMS diagnosis, such as poor echogenic parts, mixed echogenic, central necrosis, irregular vessel distribution on color Doppler, high peak systolic velocity and low impedance to flow. Unfortunately, these characteristics are also present in benign myomas [39].

Exacoustos *et al.* evaluated 257 patients by the preoperative gray scale and color Doppler sonographic findings, including 225 leiomyomas and 8 LMS. US markers significantly associated with LMS presence were: lesion diameter > 8 cm, solitary lesion, presence of cystic degeneration and increased peripheral and central vascularity. A combination of these findings leads to a sensitivity rate of 100% and specificity of 86% [40].

Magnetic Resonance Imaging (MRI) is a suggested examination in difficult cases where the diagnosis of suspect LMS is not clear. Unfortunately, the MRI cannot provide a final diagnosis of LMS, since the absence of ill-defined margins and calcifications [41] and a high signal intensity are not significantly associated to LMS [42]. Only two small investigations on LMS by gadolinium contrast and MRI slides on 40-60 seconds after injection, reported positive predictive values of 53 to 100% and specificities of 93 to 100% [43, 44]. Also computed tomography (CT) failed in the differential diagnosis between LMS and myomas [45].

The proposed methods to investigate, in preoperative time, the myoma characteristics were: 1) Dynamic MRI with serum measurement of lactate

dehydrogenase (LDH-3) levels; 2) the F-fluorodeoxyglucose (FDG) CT/Positron Emission Tomography (PET). The CT/PET by FDG did not provide brilliant results in the differential diagnosis between LMS and myomas, since the FDG uptake changes in cancers [46].

LMS diagnosis can be achieved with certain only with the histological analysis of the entire surgical specimen; also, frozen section analysis provided poor diagnostic results, because the cancer can be present only in a small part of the uterine mass and analysis typically depends upon a limited tissue sample [46, 47].

While, at MRI evaluation factors significantly associated with LMS included single and large tumor, non-myometrial origin, poorly defined margins, thickened endometrium, peritoneal implants, intermediate or high signal intensity in T1 or T2 sequences, heterogeneous T1 signal, cystic alteration of the tumor and heterogeneity of the tumor's enhancement ($p< 0.05$) [47].

In fact, in case of definitive histologic LMS diagnosis, there is a high likelihood of false negative results in frozen section analysis [48,49]; thus, only the final histology of LMS should influence successive surgery [50].

FIBROIDS, SERUM MARKERS AND PREDICTION OF MALIGNANCY

Current literature does not report any specific serum markers helpful to differentiate between uterine fibroids and sarcomas are available [51]. Patsner *et al.*, in 1988, reported a possible correlation between preoperative serum CA125 levels and LMS spread [52]. They evaluated 27 women affected by LMS (24 with primary disease and 3 with recurrence) and found that 21.4% of these, in surgical stage I-II and 80%in surgical stage III-IV, had an elevated serum CA125 value. Duk *et al.* [53] successively confirmed these results, evaluating thirty patients diagnosed for LMS: 40% had elevated serum CA125 levels before treatment. The CA125 high serum levels was correlated with extrauterine disease (67% of patients with elevated serum CA125 had extrauterine tumor spread versus 33% with normal serum CA125) and with negative prognosis. Recently, other authors confirmed these data [54, 55], however the populations involved are really small [56].

Other researchers have sought to identify other biological factors to be investigated as markers of LMS.

Kim *et al.* [57] compared serum CA125with Neutrophil Lymphocyte ratio (NLR) value, as preoperative diagnostic markers for LMS. They showed that an NLR ≥2.12 had 74.5% sensitivity and 70.3% specificity for the preoperative diagnosis of LMS, whereas serum CA125 ≥ 27.5 U/mL had 52.3% sensitivity and 50.5% specificity.

Cho *et al.* [58] reviewed, retrospectively, 31 women affected by LMS and compared, by multivariate analysis, them with 93 patients with fibroids. They resulted a reporting BMI ≤ 20, NLR > 2.1 and largest-lesion diameter > 8 cm as independent preoperative predictive factors of LMS, with a sensitivity and specificity ranging between 41-63.6% for BMI, 78.8-82.8% for NLR and 41.0% and 82.4% for largest lesion, respectively.

Nevertheless, the serum lactate dehydrogenase (LDH), an enzyme elevated in case of tissue necrosis, was evaluated in patients diagnosed for LMS; in fact, Seki K *et al.* [59] showed an LDH increase in patients affected by LMS. Recently, tumor markers used, to evaluate biological seral levels in LMS patients, were total LDH and its isozymes, reporting total LDH and LDH3 as the best negative predictive value for LMS (respectively 100 % and 99.2%) [43].

Nagai *et al.* [60] applied to 63 patients, suspected for LMS, the PRE-operative Sarcoma Score (PRESS): This score included the LDH evaluation and consisted of a maximum total of 7 points (1 point for positive MRI findings and 2 points each for age, serum LDH values, and cytological findings). In the screened population, 15 patients had a malignant disease. In their analysis, the difference between two groups was statistically significant for LDH and MRI findings, but not for CA125. The sensitivity and specificity of PRESS score resulted 73% and 100% respectively for a value up to 4.

ASYMPTOMATIC FIBROIDS MANAGEMENT

Basing on current literature, an annual clinical and US follow-up (Figure **20**) seems to be sufficient until menopause. In post-menopausal period, fibroids generally stop growing and are highly unlikely to become symptomatic.

Fibroids should be adequately investigated in case of symptoms and if they correlate to a suspicion of malignancy, when fibroids size becomes difficult to investigate by ultrasound and MRI.

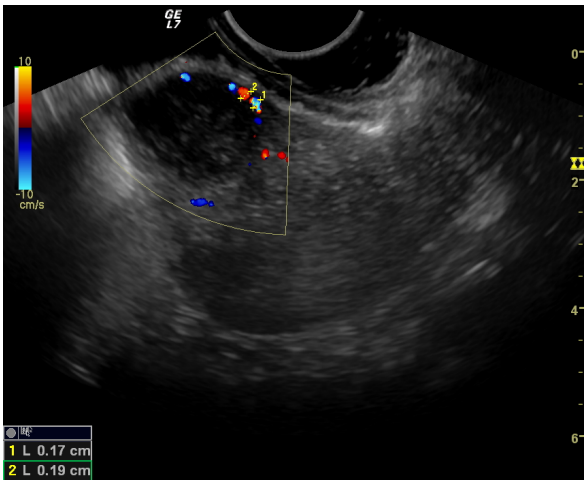

Figure 20: An ultrasonographic transvaginal scan image showing a fundal subserosal fibroid.

About the possible surgical approach to propose in patients with fibroids, it should be always including: the fibroids' growth, the fibroids size, any suspicion of malignancy, the US imaging, infertility and woman's fertility plans. All reported evidences suggest that the fibroid presence, in particular large or multiple lesions, has been associated with an increased risk of infertility and, in case of pregnancy, with a significant enlarged risk of miscarriage, fetal malpresentation, placenta previa, preterm birth, cesarean section and postpartum hemorrhage. However, controversies about the most accurate parameters to exclude malignancy at imaging technique still exist and no definitive imaging predicting features of malignancy for uterine fibroids have been defined. Nonetheless, the combined presence of the above-mentioned parameters and fast growing fibroids should be of alert and should induce to consider surgery.

Moreover, due to the clinical symptoms, treatment is required in approximately a third of patientswith uterine fibroids [61]

About minimally invasive treatments proposed for fibroids' management there are two options: the transcervical radiofrequency ablation of fibroids and uterine artery embolization (UAE) for fibroid treatment.

The first option is based on the Sonata System (previously called VizAblate), providing transcervical radiofrequency ablation. It has been shown, through the results of the FAST-EU Trial, to reduce leiomyoma volume, decrease heavy menstrual bleeding, and improve health utility scores in women with symptomatic leiomyomas [62-64]. Another recent article described results through 12 months of the Sonography Guided Transcervical Ablation of Uterine Fibroids pivotal trial [65] performed on 1-10 leiomyomas per patient with leiomyoma diameters ranging from 1 to 5 cm. Coprimary endpoints assessed at 12 months were reduction in menstrual blood loss and absence of surgical reintervention. Additional assessments included symptom severity, quality of life, patient satisfaction, reductions in uterine and leiomyoma volumes, and safety. Transcervical ablation [65] was associated with a significant reduction in leiomyoma symptoms with no device-related adverse events and a low surgical re-intervention rate through 12 months, demonstrating its potential to safely and effectively treat all non-pedunculated leiomyoma types through a uterus-conserving, incisionless approach.

The decision to recommend UAE should be made by interventional radiologist in collaboration with a gynecologist who has already discussed the various medical and surgical options with the patient and absolute contraindications for UAE include viable pregnancy, active infection, allergy to contrast agent and suspected uterine, cervical, or adnexal malignancy. Several reports have demonstrated the safety and efficacy of UAE in fibroids larger than 10 cm and the UAE is traditionally performed with moderate sedation via a right common femoral artery approach with embolization of bilateral uterine artery [66]. More recently, trans-radial access (TRA) has gained popularity for UAE with the apparent advantage of allowing patients to move freely following the procedure to assume the most comfortable position. Following UAE, a substantial inflammatory process manifests resulting in the post-embolization syndrome consisting of pain, low-grade fevers, nausea, vomiting, and malaise [65].

The expected outcomes following a UAE include 50 to 60% fibroid size reduction, 40 to 50% uterine size reduction, 88 to 92% reduction of bulk symptoms, greater than 90% elimination of abnormal uterine bleeding, and 80 to 90% patient satisfaction, and at 3-year follow-up, the overall reintervention rate among patients who underwent UAE was 14.4% [67].

Complications following UAE can include a permanent amenorrhea (0–3% for women younger than 45 years, 20–40% for women older than 45 years), a prolonged vaginal discharge (2–17%), the fibroid expulsion (from 1.7 to 50% of cases), septicemia (1–3%), pulmonary embolus (<1%), and nontarget embolization (<1%) [67]. Less common complications include infection, delayed contrast material reactions,

urinary tract infection or retention, and nerve or vessel injury at the access site, with a risk of hysterectomy in less than 1% of patients [67].

Pharmacological treatments include oral contraceptives, progestins, and the levonorgestrel releasing intrauterine systems, but they are used 'off-label' since not indicated for management of uterine fibroids because fibroids are progesterone sensitive. Moreover, the levonorgestrel-releasing intrauterine system is contraindicated in the case of fibroids that distort the uterine cavity.

GnRH agonists, which trigger a temporary biochemical menopause, reducing in the progesterone and oestrogen levels and inducing amenorrhea; their preoperative administration also leads to a hemoglobin increase, a reduction of the size of the fibroids. Because of their side-effect profile, with climacteric complaints and reduced bone density, however, they can only be used over a brief period,

not for more than 3–6 months at a time, as it has side effects (like hot flushes and vaginal dryness) and may reduce bone mineral density [68].

Control of bleeding is achieved faster with newer drugs like ulipristal acetate (UPA) than with GnRHa. The UPA is the latest anti-progestin studied in large clinical trials used to treat moderate to severe symptoms of uterine fibroids, is the mostly studied of a class of substances, the selective progesterone receptormodulators (SPRMs).

UPA has many pharmacological effects on fibroids, endometrium and hypothalamus-pituitary axis. The direct action on the fibroma of the UPA is by reducing the volume of the fibroma and inhibiting cell proliferation and induction of apoptosis, by down regulating antiapoptotic factors, antifibrotic activity, and reducing or blocking growth factor expression. The direct action on the endometrium of the UPA is due to the rapid reduction of bleeding and to the benign and reversible changes of endometrial tissue as progesterone associated endometrial changes (PAEC). The action on the hypothalamus-pituitary axis is due to the inhibition of the LH peak and the estradiol levels are maintained as in the follicular middle phase [69].

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the benefits and risks with ESMYA (UPA 5 mg, Gedeon Richter, Budapest, Hungary), following of serious liver injury, including liver failure leading to transplantation. The PRAC has concluded that ESMYA may have contributed to the development of some cases of serious liver injury. After considering all the evidence, the PRAC concluded that the medicine must not be used in women with liver problems and that certain other patients may start new treatment courses provided they have regular liver tests [70].

WHEN TREAT ASYMPTOMATIC FIBROIDS?

Treatment of asymptomatic myomas should be always indicated in case of symptoms and if the symptoms correlate to a suspicion of malignancy, when fibroids size becomes so large that scanning with ultrasound or MRI cannot define its benignity. Moreover, fibroids should be treated to enhance fertility rate in women wishing pregnancy and to reduce risk of negative outcome in pregnancy. Generally, patients with fibroids to be treated with minimally invasive surgery or methods, as fibroids' embolization or the Sonography Guided Transcervical Ablation of Uterine Fibroids should be referred in secondary centers that use these methods with experience and employ these methods on large numbers.

In addition, after fibroids diagnostic scan and adequately diagnosed by a specialist, patients could be referred to a general practitioner, in case of light symptoms, for its eventual pharmacological treatment.

In any case, a patient with uterine fibroids must always be carefully evaluated, with an adequate counselling, in order to explain and to discuss with risks and benefits of all possible management strategies.

CONCLUSIONS

Since fibroids represent the most common benign gynecological tumors and about 40-60% of patients with fibroids are asymptomatic, approximately 50% of women will seek a second opinion and no standard guidelines for the management of asymptomatic fibroids have been reported. Fibroids treatment is tailored for patients depending on: risk of malignancy, numbers, size and symptoms of fibroids (Figure **20**), women age and fertility plans. Authors suggested to treat fibroids before they grow more than 5 cm [71] (Figure **21**) and before the treatment becomes more challenging for fertility [33], even if the surgical treatment should be always performed in case of suspicion of LMS or to prevent complications related to fibroids excessive size. In case there are not these clinical problems, an observation policy is generally recommended till the onset of the menopause.

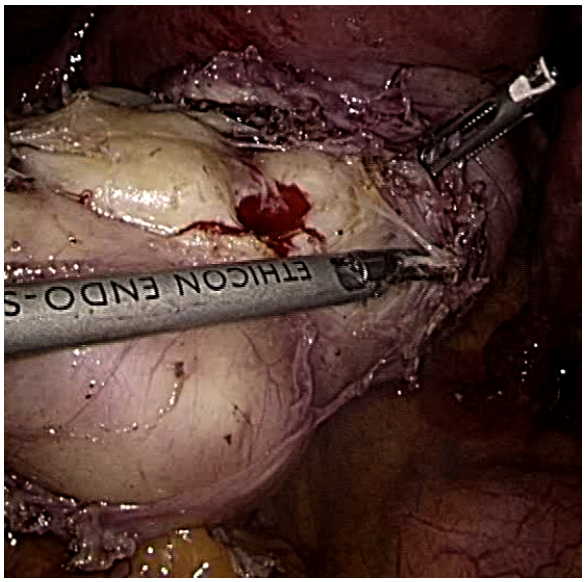

Figure 21: A laparoscopic image showing a large intramural fibroid of the uterine body, removed for symptoms.

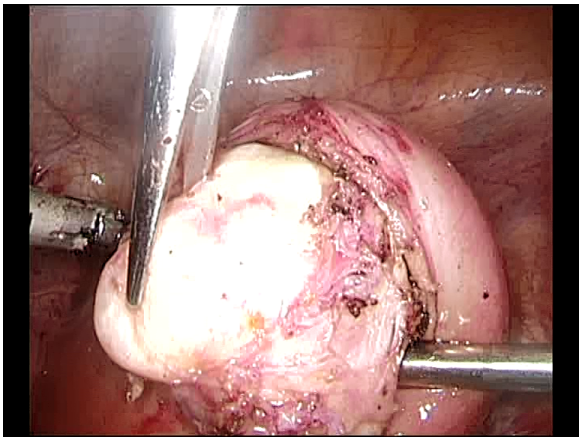

Figure 22: Laparoscopic myomectomy for a 7 cm of diameter intramural fibroid removal.

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Received on 19-11-2018 Accepted on 07-01-2019 Published on 02-04-2019

http://dx.doi.org/10.15379/2408-9761.2019.06.01.02