

# Which is the best fertility-sparing treatment for uterine fibroids? Review of literature

## Abstract

Uterine fibroids are benign tumors of the smooth muscle cells of the uterus that are the most common benign tumors in women during their reproductive years. The etiopathogenesis is multifactorial but we know that mainly estrogen and progesterone induce UF formation and growth. UF vary greatly in size, location, and symptoms: most tumors are largely asymptomatic, but they may also cause a wide range of severe and chronic symptoms that impact negatively with familiar and social relationships. UF might cause infertility. Their adverse effects on pregnancy because distort the endometrial cavity and thin the endometrium. In fact the negative action of fibroids on fertility is mainly due to produce numerous cytokines and growth factors that produce an endometrial inflammation that, with an altered local hormonal environment, may impede embryo-implantation. The type of treatment may depend on the location, size and number of UF and it should be related to understanding if the therapy improves the reproductive capacity of the woman. In this review of the literature we evaluate the various therapeutic possibilities that we have available if we decide to treat UF to improve the fertile capacity of the woman who wishes to have children. We will exclude medical therapy, which is predominantly birth control, although in recent years new substances are being studied, such as vitamin D and epigallocatechin gallate, which promise interesting therapeutic developments. A proper mention will be made of laparotomy, laparoscopic and hysteroscopic myomectomy, but particular importance will be given to the evaluation of new therapeutic trends such as high-intensity focused ultrasound, also guided by nuclear magnetic resonance, and thermal ablation with radio frequency and microwaves. The embolization of UF will also be addressed, but we know it is contraindicated for women who wish to become pregnant.

**Keywords:** uterine fibroids, hysteroscopic myomectomy, high-intensity focused ultrasound, radiofrequency myolysis, microwave thermoablation

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**Abbreviations:** UF, uterine fibroids; UFE, uterine fibroid embolization; PVA, polyvinyl alcohol; PES, post-embolization syndrome; HIFU, high-intensity focused ultrasound; FUS, focused ultrasound surgery; MRgFUS, magnetic resonance imaging guided high intensity focused ultrasound; RFM, radiofrequency myolysis; MWA, microwave thermoablation

## Introduction

Uterine fibroids (UF) or myomas or leiomyomas, are benign tumors deriving from the abnormal development of a single clone of smooth muscle cells or from alterations of immature smooth muscle cells or from totipotent mesenchymal cells. They are the most common benign tumors in women during their reproductive years, with an estimated an incidence of about 20-30% for women aged 20-30, rising to over 60% in women aged 45-49.<sup>1</sup>

In a recently published systematic review, Stewart et al.<sup>2</sup> underlined factors which increase the incidence of UF, and these are: black race, elevated BMI, age, premenopausal status, hypertension, positive family history, time elapsed since last labor, consumption of food additives, and soybean milk.

Their development process is still unclear. We know that they do not occur before puberty and that they decrease after menopause. In pregnancy they increase considerably in size to return to normal volume after childbirth and puerperium. This suggests hormonal involvement in the formation and growth of UF. Being an estrogen dependent tumor, it is affected by the action of Progesterone, even if it

is poor in receptors for Estrogen and Progesterone. Estradiol maintains Progesterone receptors and prepare the tumor to be stimulated by progesterone. Progesterone, thanks to the presence of receptors, should be the main steroid initiating uterine muscle differentiation, and its subsequent abnormal growth.<sup>3,4</sup>

Myomas vary greatly in size, location, and symptoms. 95% are located in the uterine body, 3.5% in the cervix and 1.5% in the isthmus. 70% are intramural, 20% are subserosal (sessile or pedunculated) and 10% are submucosal. Warmsteker and Coll. improved the definition of submucosal fibroids, classifying them according to their intracavitary component and development in the myometrial wall.<sup>5</sup> This classification was subsequently adopted by the European Society for Human Reproduction and Embryology (ESHRE).

In 2011 Munro and Coll. publish the PALM-COEIN classification system for the causes of abnormal uterine bleedings and includes the classification of Wamsteker and adds categorizations for every type for fibroids that are numbered from 0 (totally intracavitary) to 7 (totally subserose) in relation to the involvement of the endometrium, myometrium and peritoneal serosa. Fibroids that do not affect the myometrium (cervical, infralegamentary and "parasitic" fibroids) are classified with number 8.<sup>6</sup>

About 20% of UF are silent and are diagnosed during routine tests, but they may also cause severe and chronic symptoms. The most common symptoms include abnormal bleedings or menorrhagia, associated or not with abnormal bleedings, with secondary anemia, dysmenorrhea and deep dyspareunia, pelvic and abdominal pain and

sense of weight, gastro-intestinal disorders, infertility and obstetric pathologies (including miscarriage and premature labor).<sup>7</sup> Nearly half of women report that the UF negatively impact their relationships and quality of life, many women delay seeking care by an average of 3–5 years.<sup>8</sup>

### Uterine fibroids and fertility

Over 50% of women of reproductive age can have a UF. If we add to this consideration that, to date, the age of pregnancy research has moved much forward, more and more often we must ask ourselves the question of how to deal with this pathology which negatively impacts women's fertility.

There are many hypotheses that try to explain why fibroids can cause infertility. Fibroids have traditionally been thought to exert their adverse effects on pregnancy by get deformed the endometrial cavity, thin the endometrium and distort blood flow.<sup>6</sup> They can also obstruct the tubal hosts and the cervical canal. However, these anatomical changes are only one of the components of the negative action of fibroids on fertility, because their effect is more complex as it is determined by a molecular activation with consequent biochemical change of the surrounding environment.<sup>9</sup> UF produce abundant extracellular matrix as well as numerous cytokines and growth factors that produce an endometrial inflammation that, with an altered local hormonal environment, may impede embryo-implantation. Richlin<sup>10</sup> has shown that plasma glycodeilin levels have significantly increased in patients with uterine fibroids. Glycodeilin production is related to the increase in progesterone in the secretory phase of the menstrual cycle. High levels of proliferative and peri-ovulatory glycodeiline can compromise the implantation of the embryo. Ikhen<sup>11</sup> shows that the fibroids, especially submucosal produce a decidualization with a reduced release of cytokines and growth factors such as leukocyte inhibitory factor and cell adhesion molecules that are essential for the plant. In addition, UF alter the expression of genes responsible for implantation, such as the type II bone morphogenetic protein receptor and glycodeilin. Myomas also alter uterine contractility, interfering with sperm progression or embryo migration, especially in uterus with multiple or large fibroids which alter the shape and structure of the uterine cavity.<sup>12</sup>

The relationship between the presence of UF and reproductive disorders is difficult to define. What we can establish is that:

1. submucosal fibroids decrease fertility and increase spontaneous abortions.
2. intramural fibroids can decrease fertility but with less solid evidence: spontaneous abortions seem to increase.
3. subserous fibroids have no impact on fertility but can increase the rate of abortion.

Overall, UF still increase the risk of obstetric complications: fetal growth retardation, placenta previa, untimely detachment of the placenta, increase in the number of caesarean sections due to altered fetal situation or presentation, postpartum hemorrhages, missed secondment.<sup>13</sup>

### Therapy

The type of treatment depends on the location, size and number of UF and whether their removal can improve symptoms. When also addressing the problem of woman's infertility, it is essential to establish that it is related to fibroids and it is necessary to evaluate

how much its removal, or reduction in volume, can improve the pregnancy rate and the maintenance of pregnancy.

### Medical therapy

Medical therapy is used only to relieve the symptoms due to the presence of UF and can only be prescribed for short periods of time due to important side effects.

*GnRH-agonists* determine a menopausal-like state for an accentuated reduction of estrogen secretion. In addition to the specific symptoms of menopause (hot flashes, night sweats, moderate depressive syndrome), if administered for periods longer than 6 months they can cause bone demineralization and facilitate the onset of latent cardiovascular diseases.

*Danazol* is an androgenic agonist and can suppress fibroid growth but has little effect on volume reduction and endometrial thickness. It is hardly accepted by patients due to the high incidence of adverse effects such as acne, hirsutism, weight gain, hair loss and vaginal dryness.

*Levonorgestrel-releasing intrauterine system* can be used in patients who do not have particularly altered uterine cavity by UF, but the effect on their volume is controversial. Expulsion of the LNG-IUS is more common than in women without fibroids.<sup>14</sup>

*Ulipristal acetate* (UPA) is a selective progesterone receptor modulator that acts on progesterone receptors in myometrial and endometrial tissue and inhibits ovulation without causing large effects on estradiol levels or antigluccorticoid activity. UPA at dose of 5 mg/day for 3 months reduces abnormal bleedings and reduces the volume of UF. Treatment is aimed at women with symptomatic fibroids who were planning subsequent surgical therapy.<sup>15</sup>

European Medicines Agency (EMA) in the 2018 review, following a recent case of liver injury, which led to liver transplantation in a patient taking the drug, concluded that there is a rare but serious risk of liver injury with medicines based on ulipristal acetate when it is used to treat UF. The EMA Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that patients stop taking ulipristal acetate 5 mg for UF while the safety review is ongoing. No new patients should begin treatment with these medicines which will be suspended in the European Union during the review.<sup>16</sup>

Medical therapy for UF is mainly aimed at hypoestrogenism or blocking of estrogen or progesterone at the receptor level, interfering with ovulatory cyclicality and altering endometrial development and receptivity. This is the reason because medical therapy plays no role in the treatment of fibroids in infertile patients.<sup>17</sup>

In recent years, alternative substances to hormonal therapies are being studied and the results, although preliminary, are encouraging.

*Vitamin D* is a name of a group of steroid compounds fat-soluble. The main natural source of vitamin D is the endogenous production of cholecalciferol (vit D3) at the skin level, starting from cholesterol, through a chemical reaction that depends on exposure to sunlight. Since vitamin D can be synthesized in adequate quantities by most women sufficiently exposed to sunlight, it should not be considered a vitamin but a prohormone. Vitamin D3 (calciferol) acts in fact with a hormone-like mechanism of action, as it is autonomously synthesized by the human organism, it acts on a target organ and has a structure reminiscent of steroid hormones. Its receptors are found in various organs, including the myometrium and in fibroid tissue.<sup>18</sup> Vitamin

D is an anti-fibrotic factor, regulates cell cycle and differentiation, inhibits angiogenesis and induces apoptosis. Inhibits neoplastic transformation and tumor growth. The study of Halder shows that vitamin D3 is significantly lower in women with UF compared to normal healthy controls.<sup>19</sup> The vitamin D deficiency causes an increased expression of receptors for sex hormones in myometrial tissue and has been shown that these receptors are reduced by vitamin supplementation.<sup>20</sup> Sabry has shown in 67 women with symptomatic UF and pelvic pain that serum vitamin D levels are inversely correlated with the average volume and number of UF.<sup>21</sup> Hajhashemi et al. indicate that supplementation with 50,000 IU/week for 10 weeks reduces ultrasound-controlled UF volume by 12% without evidence of side effects.<sup>22</sup> Vitamin D could be considered a therapy aimed at symptomatic patients who for various reasons cannot undergo surgery or cannot take hormone therapy.

It can be evaluated as a pre-operative therapy for a better surgical outcome. Finally, it could be, if further studies confirm it, an excellent weapon of prevention, effective and low cost, as well as leading to a further beneficial effect on skeletal and extra-skeletal systems.<sup>23</sup>

*Vitamin D analogues* we know that vitamin D3 can, at high doses (40000 IU/day) or prolonged over time (1000 IU/day) can cause toxic phenomena (nausea, diarrhea, polyuria) or even by hypervitaminosis (hypercalcaemia and hypercalciuria, hyperphosphataemia). A possible alternative may be to resort to the use of analogues of vitamin D, of which the best known and most studied is Paricalcitol. This synthetic analogue is used to treat hyperparathyroidism. It indeed happens to reduce the synthesis and secretion of PTH, acting selectively on the receptor of vitamin D present inside the parathyroid cells. Paricalcitol reduces the cell proliferation, induces apoptosis and, in the specific case of uterine fibromatosis, it can determine the volumetric reduction of UF. Beside vitamin D, the paricalcitol can be an effective drug in the conservative therapy of UF. Of course, further, more extensive clinical trials are needed to confirm its effectiveness and security.<sup>24</sup>

*Epigallocatechin gallate (EGCG)* is a polyphenol contained in high quantities in green tea, has high antioxidant, anti-inflammatory and anti-proliferative activities. Zhang in a study,<sup>25</sup> conducted on uterine leiomyoma cells added with EGCG vs. controlled, demonstrated a reduction in cell proliferation due to the reduction in nuclear proliferative activity in kinase 4 (CDK4) and catechol-methyl transferase (COMT). The latter is an important enzyme in the conversion of hydroxy-estradiol and therefore inhibits the estrogenization of the uterine environment. Through the up-regulation modulation of apoptosis and a down-regulation of proliferation, EGCG is able to reduce cell survival. Roshdy<sup>26</sup> (recruited 33 women, aged between 18 and 50, who had at least one UF with a volume greater than 2 cubic cm. 22 women administered 400 mg/day of Green tea-extract capsules (each capsule contained 95% polyphenols and 45% EGCG) for 4 months. 11 women received identical capsules containing inert material. After 4 months the UF of women who had taken EGCG showed a volumetric reduction of 32.6% (versus a 24% increase in controls) with a marked improvement in symptoms and QoL.

Considering that the pathways of vitamin D and EGCG are sometimes the same, Porcaro and Coll.<sup>27</sup> they thought to evaluate the effectiveness of the association of these. They selected 15 women (vs. 15 controls) 18 years of age or older, in premenopausal stage, with at least one myoma  $\geq 2$  cm<sup>3</sup> with moderately or severe myoma-related symptoms. 50 mcg of vitamin D, 300 mg of EGCG and 10 mg of vitamin B6 were administered to you for 4 months. The authors found a reduction in the volume of UF of 34.7% (6.9% increase in controls)

with improvement of symptoms and QoL. The association of vitamin D with EGCG seems to be an optimal approach for the treatment of uterine fibroids and the control of related symptoms, so much so that Ceibiera and Coll say that “*as new pharmaceutical medical options emerge, natural compounds should also be considered as potential options for UF management and prevention. For example, vitamin D or EGCG should be tested in human clinical trials to establish its safety and clinical effects*”.<sup>28</sup>

## Surgical therapy

*Myomectomy* is the surgical technique that allows the removal of UF and is indicated in women who wish to retain fertile capacity. Myomectomy can be performed by laparotomy, laparoscopy or hysteroscopy, depending on the size and location of the fibroid.

In the infertile population, cumulative pregnancy rates by the laparoscopic and the mini-laparotomy approaches are similar.<sup>29</sup> Open surgery is associated with more pain and there is higher infection risk. Also there is higher chances of infertility arising due to open surgery due to formation of adhesions post-surgery.

*Laparoscopic myomectomy* is the procedure that requires a shorter hospital stay, causes less pain for the woman and there are few cases with fever as there is less chance of infection.<sup>30</sup> No evidence suggested a difference in recurrence risk between laparoscopic and open myomectomy.<sup>31</sup> During laparoscopic myomectomy it is often necessary to resort to morcellation, i.e. reduction of the UF in parts of smaller dimensions, so as to allow their extraction through the access of the trocars. This technique can involve important complications such as vascular lesions or abdominal viscera, and sometimes it can lead to the spread of fragments of leiomyoma that can transform into “parasitic” leiomyomas.<sup>32</sup> In 2014, instrumental morcellation was accused due to a case of a patient undergoing laparoscopic hysterectomy, with undiagnosed leiomyosarcoma. Subsequent FDA reporting discouraged the use of electric morcellators stressing the need for a review of the techniques of extraction of uterine tissues. In fact, the laparoscopic morcellation of a sarcoma can lead to the dissemination of the disease at the pelvic and abdominal level and a reduction in survival.<sup>33,34</sup>

*Hysteroscopic myomectomy* in the case of female infertility which leads to the need to resort to assisted fertilization (PMA), there are two factors that interfere with the success of PMA itself: the quality of the embryo and endometrial receptivity. Endometrial receptivity is a very complex process involving the anatomy of the uterine cavity, endometrial thickness, immunological and coagulation factor alterations and cytokine secretion. Bosteels<sup>34</sup> states that the existence of endocavitary pathologies can negatively influence endometrial receptivity and therefore alter the outcome of PMA, but also reduce the rate of spontaneous pregnancies.

The submucosal UF are managed hysteroscopically technique that is the “gold standard” procedure for treating submucous myoma (grade G0, G1 and G2) and represents an effective and safe solution to infertility myoma-related.<sup>35</sup> In 2005 Lasmar<sup>36</sup> and Coll. proposed a classification for the pre-surgical evaluation of submucosal UF which takes into consideration, in addition to the size of the myoma and its degree of myometrial extension, also the anatomical location within the uterine cavity and the surface extension in the wall. The classification assigns a score from 0 to 2 to the various parameters to obtain a feasibility and difficulty score for surgery.

For submucosal myomas of diameter <2 centimeters of grade G0 or G1, even at fundic localization, the hysteroscopic approach is



imperative. A diameter of the MS > 5 centimeters, associated with a fundic localization and a G2 grading, advises against hysteroscopic surgery and directs towards an abdominal approach. For intermediate classes, the surgeon will evaluate the feasibility of a hysteroscopic intervention and the technique to be adopted.

Resectoscopic myomectomy has numerous advantages over traditional laparotomy, as myometrial trauma that is significantly reduced, hospitalization times are much shorter and the risk of postoperative adhesions is practically absent.<sup>37</sup> Resectoscopic myomectomy should not be offered to women, even if infertile, with intramural UF, regardless of their size, especially if the endometrium is intact.<sup>38</sup> Complications of hysteroscopy are very rare: uterine perforation, infection, excessive bleeding and venous intravasation. Long-term complications can be summed up in the formation of intrauterine synechiae alone.<sup>39</sup>

The use of bipolar current loops has resolved some critical issues in the execution of resectoscopic myomectomy. The bipolar current loops require an iso-osmolar relaxing solution (physiological solution) which, among other things, allows a better management of the “intravasation syndrome” which occurs when there is an excess of relaxing liquid deficit with rapid absorption of this in the bloodstream. The increase in circulating blood volume can lead to reduction of diuresis and hyponatraemia and consequent pulmonary edema and cardio-circulatory failure, up to cerebral edema and coma. If we consider that the relaxing solution with glycine or sorbitol-mannitol allows a maximum deficit of 1000-1500 ml, with the physiological solution the tolerated deficit can reach 2000-2500 ml.<sup>40</sup>

### Uterine fibroid embolization (UFE)

Since 1996, when McLucas and Goodwin<sup>41</sup> performed the first UF embolization at the University of California Medical Center, about 35,000 cases have so far been treated with this technique. The technique consists of inserting a small angiographic catheter into the uterine arteries and injects a flow of tiny particles which decreases, until it stops, the blood flow towards the uterus. The uterine artery was embolized initially by injecting polyvinyl alcohol (PVA) particles followed by the infusion of a gelatin sponge stopper. The gelatin sponge cap had the task of completing the occlusion of the uterine artery, preventing the PVA particles from displacing outside the artery, resulting in embolization of other arterial structures. In more recent times, calibrated microspheres have been used which have uniform dimensions compared to PVA and embolization has become technically simpler, also reducing the possibility of clogging the microcatheter (which is a continuous problem with PVA preparations).<sup>42,43</sup>

A 2013 review and meta-analysis that the UAE's most important complications for symptomatic UF were: vaginal secretions and fever (4.0%), bilateral UAE insufficiency (4.0%) and postembolization syndrome (2.9%).<sup>44</sup>

Post-embolization syndrome (PES) is one of the most common side effects of embolization. It occurs with fever, nausea/vomiting and pain that appear within the first 72 hours after embolization to resolve, usually spontaneously, after 48-72 hours. PES is believed to be caused by tissue hypoxia and subsequent cell death resulting in the release of decomposition products and inflammatory mediators that alter adjacent normal tissues.<sup>45</sup>

Current contraindications to the UAE include pregnancy, the desire for a future pregnancy, infertility, suspicion of gynecological malignancy, anaphylactic reaction to contrast material, kidney failure

and coagulopathy.<sup>46</sup> Raiklin<sup>42</sup> by means of magnetic resonance imaging has shown that in the hours following embolization, ischemia of the body and of the uterine fundus occurs which resolves spontaneously within 72 hours. Ischemia, however transient, affects the endometrium and the internal and middle myometrial layers, causing irreversible endometrial damage (in addition to the formation of adhesions), which can be deleterious for women already diagnosed as infertile.

### New therapeutic trends

Current therapeutic interventions, to replace, supplement or mediate surgical and medical therapy conventional, include the use of tools that are based on different forms of energy for destroy, modulate, regenerate biological tissues, and on guides of different origin, frequently radiological or ultrasound, to direct the energy and effects of the treatment, as well as to verify them.

### High-intensity focused ultrasound (HIFU)

In 1927, Wood and Loomis<sup>47</sup> recognized that ultrasound could produce permanent alterations in biological systems, and this represented a starting point for all studies on the safety of their use and their therapeutic potential. The result of the interaction between ultrasonic waves and biological systems is a thermal effect: the absorption of ultrasound energy by a tissue leads to its heating. HIFU deposits localized energy and the results is a heating (65-95°C) at the focal point of the target tissue. The thermal effect resulting in tissue necrosis, apoptosis and cell death of the target, avoiding damage to the surrounding tissue. In therapy, low frequency and higher power ultrasounds are used (possibility of permanent biological effects): the range of ultrasound frequencies used in therapy ranges from 20 kHz to 3 MHz.<sup>48</sup>

Despite the evolution of knowledge on ultrasound and potential therapeutic effects, treatment of UF with HIFU (or focused ultrasound surgery [FUS]), one of the most promising and integrated uses of ultrasound therapy, it has not become as widespread and frequent as one might wait.<sup>28</sup> The main aspects that have limited its clinical application are derived from the lack of tools that guarantees the precise identification and characterization of the target, the monitoring of the injury during treatment, and identification of the effect during and after the administration of the therapy.<sup>49</sup>

Stewart and Coll<sup>50</sup> compare HIFU with myomectomy, with hysterectomy and with medical treatment. HIFU was significantly superior in terms of pain/discomfort, fever, transfusions and anesthesia-related complications. No negative effects were identified on both the skin (burning) and complications of the urinary tract and nervous system.

### Magnetic resonance imaging guided high intensity focused ultrasound (MRgFUS)

Magnetic resonance imaging represents a technique capable of offering high spatial resolution and anatomical detail, regardless of the type of tissue analyzed. It offers a truly complete diagnostic possibility, which is associated with a treatment planning, real-time monitoring of the lesion under treatment and an optimal post-treatment evaluation. The combination of HIFU treatment and MRI guidance has led to the creation of a system that applies as an instrument of surgery or imaging-mediated therapy ideal for many pathologies. Although this had previously been theorized and discussed, the HIFU-MRI merger took place in 1991, when the original equipment was assembled at the University of Arizona by MR FUS (MR-g-FUS)<sup>39</sup> and the indication for the treatment of fibroids was approved by the FDA in 2004.

MRgFUS provides continuous MRI imaging of UF and adjacent structures (intestine, bladder and sacral nerves) and provides continuous temperature monitoring to optimize effective tissue clotting. A low incidence of infectious complications and febrile morbidity has been demonstrated, since the coagulated thermal fibrous tissue is easily absorbed by the body.<sup>51</sup> Verpalen's review<sup>52</sup> indicates that the mean reduction in symptoms at 12 months was 59.9% and the shrinkage of UF was 37.7%. The number of adverse events was low (8.7%). The rate of reoperation at 3-33.6 months follow-up ranged from 0 to 21%. The number of reoperations tends to increase in times over 4 years. Overall, MRgFUS is associated with a low risk of post-procedural complications.<sup>53</sup> Sang-Wook Yoon,<sup>54</sup> demonstrates that MRgFUS treatment may be a good option for patients previously treated with UAE.

Data on the effect of MRgFUS/MR-HIFU treatment on fertility and pregnancy in women with UF are scarce. Rabinovici et al. and of Zou et al.<sup>55,56</sup> have shown that treatment with this technique does not alter fertility, it reduces waiting times in search of pregnancy which improves outcomes. MRgFUS/MR-HIFU appears to be an interesting minimally invasive alternative for women with UF who wish to conceive and deliver after the procedure. In fact, this technique does not increase the rate of spontaneous abortions or pregnancy complications: there is no increase in premature births, IUGR, uterine rupture or preeclampsia.<sup>57</sup>

### Radiofrequency myolysis (RFM)

Myolysis is the degenerative dissolution of muscle fibrocells. Radio Frequency (RF) is the number of waves/second that propagate in circuits or electronic systems that process and manage high frequency electromagnetic signals. RF energy, and the heat generated, causes localized coagulation necrosis in a restricted area of tissue. Thanks to electrical devices such as an antenna or an electrode, there is the possibility of generating electromagnetic waves and radiating them into space at the speed of light; the latter are called radio waves. RF, or radio waves, has wavelengths ranging from less than one centimeter to more than 100 kilometers. By applying RF in the human body, it happens that radioelectric waves exploit the thermal energy that the tissues, when hit by the waves, are able to produce.<sup>58</sup>

Radiofrequency myolysis (RFM) has been widely studied as a treatment option for UF, after a long and consolidated experience in the treatment of hepatocellular carcinoma and other soft tissue neoplasms. For more than 15 years we have known that coagulation necrosis of UF determined by radio frequency energy can lead to a reduction in their volume and an improvement, until resolution, of the symptoms.<sup>59</sup>

All the current RF devices we have available have the same therapeutic effect. There were no significant differences in efficacy based on the use of bipolar electrodes compared to monopolar ones, the use of a single antenna compared to the use of multiple antennas, the surgical route used (transabdominal, transcervical, transvaginal), the technique used for real-time visualization (laparoscopy, ultrasound) and the hardware and software that regulate the supply of energy to the tissues. What is evident is that energy-based hyperthermic systems are safe and effective and can improve a woman's quality of life.<sup>60</sup>

One of the most important problems in radiofrequency therapy was the difficulty in determining the amount of energy to be delivered to achieve safe and effective ablation. Creating multiple probe insertion sites within a fibroid is one way of maximizing the volume of ablation, which leads to a significant reduction in the fibroid,

which is sufficient to alleviate symptoms and reduce the recurrence rate. But an exaggerated energy supply could increase the possibility of myometrial weakening with the risk of uterine rupture during pregnancy.<sup>61</sup>

To overcome these problems, the use of RF delivery systems with a "volumetric" approach was used. This approach allows a myolysis with only one or two insertions of the electrodes in the UF, under ultrasound guidance, with a programmable energy supply based on the size and location of the UF.<sup>60</sup> This technique, which we will define as volumetric, eco-guided hyperthermic myolysis, creates a high level of safety, significantly reducing the risk of uterine rupture or other negative effects on future pregnancy.

### Microwave thermoablation (MWA)

Microwaves (MWs) include electromagnetic radiation in the spectrum electromagnetic are placed between radio waves and infrared radiation, with frequencies between 300MHz and 30GHz and wavelength between 1cm and 1m. The creation of an oscillating electromagnetic field induces a continuous oscillation of dipolar molecules or space charges in a dielectric material which tend to align with the oscillating electric field. The intermolecular friction due to frequent impacts between the molecules transforms the kinetic energy into heat, giving rise to a heating action. Heating obtained by producing friction and heat induces cell death through coagulation necrosis.<sup>62,63</sup>

Yang in 2014<sup>64</sup> used MWA to treat UF and had ablation rates of up to 89%. Furthermore, after 3, 6 and 12 months of treatment, fibroids decreased by an average of 61.8%, 78.7% and 93.1%. Anemia caused by excessive genital bleeding was also reduced or disappeared in 99% of patients.

A multicenter study conducted on 344 women with uterine leiomyomas in China by Hui Liu<sup>65</sup> showed that the volume of myomas decreased significantly after treatment with MWA, with a reduction rate after 6 months from ablation of 78.5%. Submucosal and intramural UF that distort the endometrial cavity, as we have already discussed, can alter fertility or cause miscarriage. The study confirms that MWA treatment, under ultrasound guidance, can effectively coagulate UF and sometimes reduce their volume until they disappear, with consequent restoration of normal uterine volume. The necrotic tissues of the treated fibroids can be expelled from the vagina even several months after therapy. Some patients conceived 20 or 30 months after therapy.

It is essential to carry out thermal ablation under continuous ultrasound control in order to prevent damage to a large area of the endometrium. In addition, the real-time control allows a localized ablation, focused on the lesion that is to be treated, making the pelvic vascular structure safe and not affecting the ovarian function. In fact, after treatment, patients' menstrual cycles remain normal.

Finally, we can confirm what Zhang Bing-Song<sup>66</sup> claims: MWA is an effective and convenient minimally invasive therapy to treat UF of type G1-6 of FIGO, specifically aimed at those patients who wish to maintain their capacity reproductive. MWA has the additional benefit of rapid post-operative recovery and a significant improvement in the quality of life of patients.

### Conclusions

In this review of the literature concerning UF therapies in women who wish to maintain their fertile capacity, a very small space is

dedicated to medical therapy because this is burdened with important side effects, if used for long periods of time, and because it has mainly contraceptive activity (the therapeutic capacity of vitamin D and epigallocatechin gallate is currently being studied, but the data available to us has not yet been validated). Laparotomy or laparoscopic myomectomy are certainly effective surgical techniques but often involve pelvic adhesion sequelae and are sometimes burdened by abundant blood losses that lengthen the time of hospital stay and the resumption of normal daily activities. In addition, the waiting time required to start a new pregnancy is long (6-8 months). Hysteroscopic myomectomy is certainly effective but is limited to FIGO G0, 1 and 2 myomas only. Sometimes type 2 requires a second surgery for complete removal. Embolization of UF, although it is an effective technique, according to many authors is not indicated for women who try to get pregnant because it can cause serious complications during pregnancy. Certainly a lot of space should be devoted, in clinical practice, to thermal ablation techniques, both with focused high intensity ultrasound, possibly under the guidance of magnetic resonance imaging (but it is a technique that needs advanced technology and is very expensive), either with the energy of radio frequency or microwaves. These are minimally invasive, safe and effective therapies and can be performed both transcervically, transvaginally and laparoscopically. Thermoablative techniques have the advantage of rapid recovery and significantly improve the quality of life of patients. A technological improvement, in the future, will make it possible to place thermal ablation in the first place in the ranking of therapy techniques for women suffering from UF who wish to keep their fertility intact.

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## Conflicts of interest

None.

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