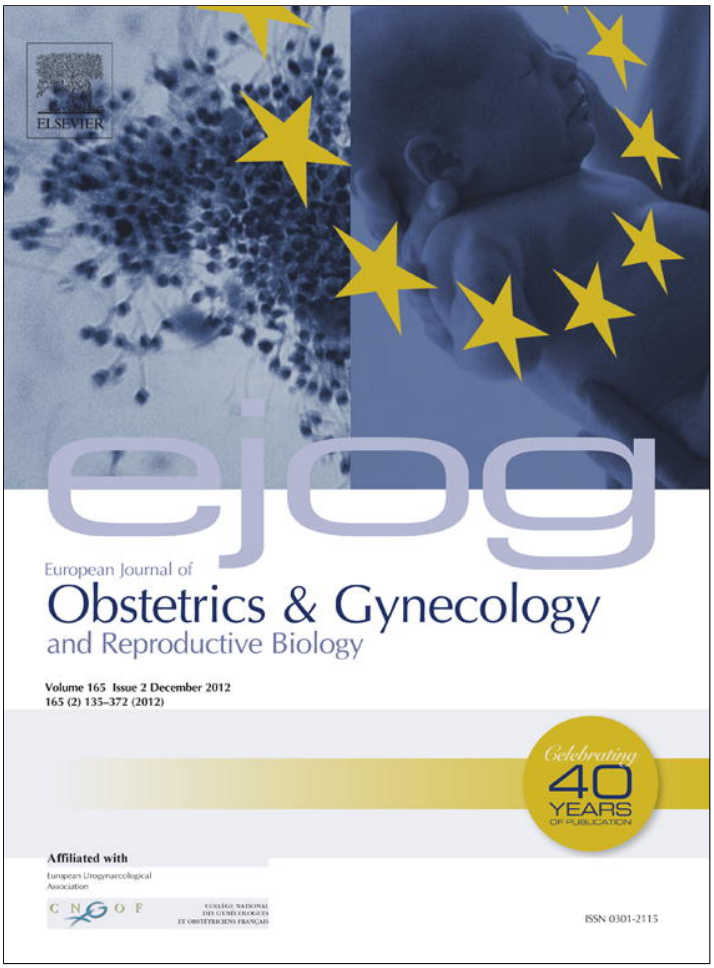

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Review

Therapeutic management of uterine fibroid tumors: updated French guidelines

Henri Marret [a,*], Xavier Fritel [b], Lobna Ouldamer [a], Sofiane Bendifallah [c], Jean-Luc Brun [d], Isabelle De Jesus [e], Jean Derrien [f], Géraldine Giraudet [g], Vanessa Kahn [h], Martin Koskas [i], Guillaume Legendre [j], Jean Philippe Lucot [g], Julien Niro [k], Pierre Panel [k], Jean-Pierre Pelage [l], Hervé Fernandez [c]

[a] Service de gynécologie, Centre Hospitalier Régional Universitaire de Tours, Hôpital Bretonneau, 2 boulevard Tonnelé, 37044 Tours, France
[b] Service de Gynécologie-Obstétrique et Médecine de la Reproduction, CHU de Poitiers, 2 rue de la Milétrie, 86000 Poitiers, France
[c] Département de gynécologie-obstétrique, Hôpital universitaire du Kremlin Bicêtre, 78 avenue du Général Leclerc, 94275 Le Kremlin Bicêtre, France
[d] Service de gynécologie-obstétrique, Hôpital Pellegrin, 33076 Bordeaux, France
[e] Service de Gynecologie-Obstétrique, CH Grasse, Chemin Clavary, 06130 Grasse, France
[f] Collège de Gynécologie Rhône-Alpes, 46 cours Président Franklin Roosevelt, 69006 Lyon, France
[g] Pôle femme-mère-nouveau-né, hôpital Jeanne de Flandre, CHRU Lille, avenue Eugène Avinée, 59037 Lille cedex, France
[h] 5, avenue Emile Deschanel, 75007 Paris, France
[i] Service de Gynécologie Obstétrique, Hopital Bichat, 75018 Paris, France
[j] Service de Gynécologie-Obstétrique, Hôpital de Bicêtre, Assistance Publique des Hôpitaux de Paris, Le Kremlin Bicêtre F-94270, France
[k] Service de gynécologie-obstétrique, centre hospitalier de Versailles, hôpital André Mignot, 177 route de Versailles, 78157 Le Chesnay, France
[l] Service de Radiologie, CHU de Caen, avenue de la Côte de Nacre, 14033 Caen cedex 9, France

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ABSTRACT

The medical management of symptomatic non-submucosal uterine fibroid tumors (leiomyomas or myomas) is based on the treatment of abnormal uterine bleeding by any of the following: progestogens, a levonorgestrel-releasing intrauterine device, tranexamic acid, nonsteroidal anti-inflammatory drugs, or GnRH analogs. Selective progesterone receptor modulators are currently being evaluated and have recently been approved for fibroid treatment. Neither combined estrogen–progestogen contraception nor hormone treatment of the menopause is contraindicated in women with fibroids.

When pregnancy is desired, whether or not infertility is being treated by assisted reproductive technology, hysteroscopic resection in one or two separate procedures of submucosal fibroids less than 4 cm in length is recommended, regardless of whether they are symptomatic. Interstitial, also known as intramural, fibroids have a negative effect on fertility but treating them does not improve fertility. Myomectomy is therefore indicated only for symptomatic fibroids; depending on their size and number, and may be performed by laparoscopy or laparotomy. Physicians must explain to women the potential consequences of myomas and myomectomy on future pregnancy.

For perimenopausal women who have been informed of the alternatives and the risks, hysterectomy is the most effective treatment for symptomatic fibroids and is associated with a high rate of patient satisfaction. When possible, the vaginal or laparoscopic routes should be preferred to laparotomy for hysterectomies for fibroids considered typical on imaging. Because uterine artery embolization is an effective treatment with low long-term morbidity, it is an option for symptomatic fibroids in women who do not want to become pregnant, and a validated alternative to myomectomy and hysterectomy that must be offered to patients.

Myolysis is under assessment, and research on its use is recommended. Isolated laparoscopic ligation of the uterine arteries is a potential alternative to uterine artery embolization; it also complements myomectomy by reducing intraoperative bleeding. It is possible to use second-generation techniques of endometrial ablation to treat submucosal fibroids in women whose families are complete. Subtotal hysterectomy is a possible alternative to total hysterectomy for fibroid treatment, given that by laparotomy the former has a lower complication rate than the latter, while by laparoscopy, these rates are the same.

In each case, the patient is informed about the benefit and risk associated with each therapeutic option.

* Corresponding author at: Pole de Gynécologie, Obstétrique, Médecine fœtale et Reproduction humaine, Hôpital Bretonneau, 37044 Tours cedex 1, France. Tel.: +33 02 47 47 47 41; fax: +33 04 47 47 92 73.
E-mail address: marret@med.univ-tours.fr (H. Marret).

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Contents

1. Introduction

Fibroids remain the most common female disease; they cause abnormal uterine bleeding (heavy or irregular menstrual bleeding, which is the main reason for gynecologic consultations of women aged 40–50 years) and also pelvic pain. They are the leading cause of hysterectomy in France. Because the last clinical practice guidelines date back to 1999, the Collège National des Gynécologues et Obstétriciens Français (CNGOF) decided to update them to take into account diagnostic and technical advances over the past decade. The development of these guidelines required the coordinators to define the questions, choose a team to answer them, and determine the levels of evidence and grades of each recommendation for physicians seeking to practise evidence-based medicine. A selection of the principal references is listed at the end [1–49].

All professionals should understand the importance of guidelines – of producing, updating, disseminating and following them – in a period when the onset of complications can require us to justify our practices. Obviously, these guidelines are not enforceable, but each physician knows that professional guidelines or recommendations are a guide to good practices [50].

This new version of these guidelines has especially sought:

- to redefine the role of medical treatment, which does not act directly on fibroids, but rather on their symptoms;
- to reconsider the role of fibroids in fertility and in infertility;
- to define the role of new alternatives to surgery for the treatment of fibroids, in relating them to new issues of the 21st century, which include the desire to retain the uterus for as long and as reproductively functional as possible, in accordance both with patients' wishes and with the potential of various new reproductive technologies and techniques;
- and to reconsider, in the light of these new surgical techniques, the real role of each indication for surgery.

The guiding principle remains that only symptomatic fibroids should be treated, for data sufficient to justify a recommendation for non-symptomatic fibroids do not currently exist.

2. Methods

The sponsor (CNGOF) designated a Scientific Committee responsible for selecting the experts/authors, defining the questions and synthesizing recommendations from their work. The questions concerned (1) the medical treatment of symptomatic uterine leiomyomas, (2) the indications for myomectomy, (3) the alternatives to surgery, and (4) the role of subtotal hysterectomy.

The experts analyzed the existing scientific literature on each subject to respond to the questions. The summary of the valid scientific data for each question included a level of evidence (LE), based on the quality of the data available and defined according to the key developed by the National Authority for Health (HAS, Haute Authorité de Santé) (LE1: high-power randomized

comparative trial or meta-analysis of randomized comparative trials; LE2: lower-power randomized trials, well-conducted non-randomized comparative studies, and cohort studies; LE3: case–control studies; and LE4: non-randomized comparative studies with substantial bias, retrospective studies, cross-sectional studies, and case series).

The Scientific Committee summarized the practice guidelines from the responses provided by the experts/authors. Each of these guidelines also includes a grade that is a function not only of the evidence level, but also of the expected clinical benefit and the ethical issues. An A grade represents established scientific proof, a B grade represents a scientific presumption, and a C grade is based on a low level of evidence, generally LE3 or LE4. In the absence of conclusive scientific proof, some practices have nonetheless been recommended based on the agreement of all members of the working group (professional consensus). Recommendations based on professional consensus were limited to the strict minimum.

All of the texts as well as the summary of the guidelines were reread by external readers, physicians from the different specialties concerned and from diverse practice settings (public, private, university or non-university). Following these revisions, we made further modifications. The methods, texts by the experts/authors, synthesis of the recommendations together with an introduction by CNGOF coordonator Hervé Fernandez, have already been published in French [51–61].

3. Question 1: medical treatment of symptoms associated with uterine leiomyomas

3.1. General framework

No currently validated medical treatment is capable of making fibroid tumors disappear (LE1). Accordingly, in cases of asymptomatic fibroids, there is no reason to consider medical treatment (grade A). In cases of symptomatic fibroids (pain or bleeding), the only objective of medical treatment is to treat the symptoms associated with them (grade C). Nonetheless the first-line treatment for symptomatic submucosal fibroids is surgical management and not medication exclusively (grade B).

3.2. Available medical treatment [1–9]

3.2.1. Progestogens

The prescription of progestogen treatment is intended to reduce heavy menstrual bleeding by reducing the endometrial hyperplasia associated with fibroids (LE2). Oral progestogens are reported to reduce their symptoms or prevalence by 25–50%, whether taken during the second part of the cycle or as 21-day contraceptives; there are no data about continuous administration. Levonorgestrel intrauterine devices (LNG-IUDs) have been shown to reduce bleeding and restore hemoglobin levels in patients with fibroids (except those that are submucosal) (LE2) [2008 CNGOF Guidelines].

Progestogens are not a treatment for fibroids, but can be used to treat the abnormal uterine bleeding associated with them for a short or intermediate period (grade C). Progestogen treatment of the heavy bleeding associated with fibroid tumors, administered by the endouterine route (LNG-IUD), has been validated and can be recommended (grade B).

3.2.2. Antifibrinolytic agents

Local fibrinolysis maintains the heavy menstrual bleeding associated with uterine fibroids. Tranexamic acid is efficacious in treating it (LE2) and can therefore be prescribed (grade B).

3.2.3. Non-steroidal anti-inflammatory drugs (NSAIDS)

These may reduce heavy menstrual bleeding but less effectively than tranexamic acid, danazol or the LNG-IUD (LE1). They are effective for the pain associated with the aseptic necrobiosis of a leiomyoma (LE2). NSAIDs can be prescribed to treat symptoms associated with fibroids (grade B).

3.2.4. GnRH analogs

GnRH analogs can be used for preoperative management, but only for short periods because of their side effects. They reduce bleeding and restore hemoglobin levels to nearly normal before surgery (LE1). A prescription lasting 2–3 months, corresponding to the marketing authorization, appears sufficient (LE1).

The addition of tibolone to GnRH agonists does not impair the improvement of the symptoms associated with fibroids and provides an identical reduction in fibroid volume (LE1). Its use can limit the side effects commonly encountered with these GnRH agonists (LE1). Addback therapy using estrogens produces a smaller reduction in fibroid volume than do agonists alone (LE3). Adding raloxifene does not impair the benefits of agonist treatment but also does not prevent the onset of hot flushes (LE2).

Leuprorelin and triptorelin are also preoperative treatments for uterine fibroids associated with anemia (Hg $<$ 8 g/dl) or when the size of the fibroid must be reduced to facilitate or enable endoscopic or transvaginal surgery (grade A). The duration of this preoperative treatment is limited to 3 months. Addback therapy with estrogens or raloxifene is not indicated, but tibolone can be added (grade B).

3.2.5. GnRH antagonists

GnRH antagonists at an efficacious dose reduce uterine volume without reducing the fibroid volume on D28. Similarly, although they do not improve the hemoglobin level on D28, their use does result in regression of menorrhagia/dysmenorrhea (LE2). They are not considered to be a treatment for fibroids. There is no contraindication to using GnRH antagonists for assisted reproduction in patients with uterine fibroids (grade C).

3.2.6. Danazol

Danazol is effective in the short-term (less than 3 months) for the reduction of symptoms associated with uterine fibroids, but no study has assessed its efficacy in the long term (more than 6 months). It appears to be less effective than the GnRH agonists and to be associated with more side effects (LE2). The use of danazol for fibroids is impeded by its side effects and its short duration of efficacy; it is not recommended (grade C).

3.2.7. Aromatase inhibitors

The aromatase inhibitors currently include letrozole, anastrazole and exemestane. They are thought to act rapidly and efficaciously against fibroid symptoms and to reduce tumor volume (LE3). Outside of research, aromatase inhibitors are not currently indicated for fibroid treatment.

3.2.8. Antiprogesterone and selective progesterone receptor modulators (SPRMs)

Mifepristone reduces fibroid size and improves the symptoms associated with them (LE1). The possibility of endometrial hyperplasia requires prudence. A dosage of 5 mg/day yields results similar to those of 10 mg/day (LE1) and may reduce this risk (LE2).

The selective progesterone receptor modulators (SPRM, including CP8947, onapristone, CDB 2914, ulipristal and asoprisnil) are currently being evaluated for the treatment of fibroids. Phase IIb trials have shown their efficacy after 3–6 months of use in reducing symptoms, the anemia associated with fibroid bleeding, and tumor

volume (LE2) [8,9]. Amenorrhea seems frequent. Ulipristal is completing phase III trials for this indication.

In the absence of a marketing authorization, which is expected in 2012–2013 in different European countries, there is not yet any indication that uterine fibroids should be treated by mifepristone or by SPRM except in research settings.

3.3. Specific situations

3.3.1. Fibroids and contraception (except IUDs)

The literature contains no evidence suggesting that oral contraceptives promote the onset or growth of uterine fibroids – not classic combined oral contraceptives, second or third generation contraceptives (doses of 20 or 30 μg ethinyl-estradiol), or progestogen-only contraceptives (LE3). Fibroids are not a contraindication to combined or progestogen-only contraceptives or to morning after pills (grade C). Conversely these contraceptives are not a treatment for fibroids (grade C).

3.3.2. Fibroids and hormonal therapy for menopause

Asymptomatic fibroids are not a contraindication to hormone therapy (grade C) because it has not been shown that this therapy promotes fibroid growth. It does, on the other hand, increase the risk of heavy bleeding in women with submucosal fibroids (LE3).

3.3.3. Fibroids and intrauterine devices

Because of the increased risk of hemorrhagic complications and expulsion, submucosal fibroids are a relative contraindication to IUDs (grade C). LNG-IUDs significantly reduce the bleeding associated with all but submucosal fibroids (LE2) and are therefore recommended in this indication (grade B).

In conclusion and in all cases before medication is prescribed for fibroids, a personalized risk-benefit analysis must be conducted and take into account the potential side effects and complications of these medical treatments.

4. Question 2: myomectomy [10–24]

Patients undergoing a myomectomy must be informed of the risk that the symptoms will persist and that the leiomyomas may recur and require further surgery (grade A). For laparotomic or laparoscopic myomectomies, and if the woman might become pregnant later on, information should also be provided about the risk of uterine rupture during a future pregnancy. The obstetrical team will consider the surgical report and any complications of the intervention for its final determination of the mode of delivery.

The literature contains no data about the management of asymptomatic fibroids or about a threshold size at which treatment should be envisioned. Nonetheless, the aggressiveness and risk level of both surgery and alternative treatments will increase with uterine volume for larger fibroids (>10 cm before menopause) (LE3). Regular follow-up therefore seems reasonable to assess the growth kinetics for asymptomatic fibroids exceeding that size before the menopause.

4.1. Role of myomectomy in women not being treated for infertility or who wish to retain their fertility *(for those who are not infertile, but want to become pregnant, or do not want to become pregnant but only to retain and optimize the possibility)*

An association has been observed between infertility and fibroids (LE2), but the responsibility of these leiomyomas for infertility has yet to be demonstrated. This association can be explained, at least in part, by the woman's age when attempting conception. That is, the incidence of both fibroids and of infertility increases with age.

4.1.1. For submucosal fibroids

Symptomatic: Complete hysteroscopic resection of submucosal fibroids effectively treats heavy menstrual bleeding in women with a normal-sized uterus and a submucosal fibroid less than 4 cm that is predominantly intracavitary (LE3). Results are less good in other conditions, but can be improved by preparation with GnRH agonists or by repeated resections (LE4). Therefore the 2008 recommendation for intracavitary fibroids has not been changed: complete hysteroscopic resection is a first-line treatment for symptomatic and submucosal fibroids of types 0, 1 (grade B) and 2 (grade C) up to 4 cm (grade C); it is possible for fibroids of 4–6 cm. A two-stage resection is recommended for submucosal fibroids if the first resection is incomplete. The thickness of the residual posterior myometrial wall in front of the serosa must be measured and a threshold of 5 mm (the most common criterion in the literature) applied to avoid complications. The reported risk of rupture of the gravid uterus after hysteroscopic myomectomy is close to zero (LE4).

Asymptomatic fibroids, discovered only on imaging: Fertility can be improved by hysteroscopic treatment for women with asymptomatic submucosal fibroids that deform the uterine cavity but are asymptomatic (LE1). Their complete hysteroscopic resection is thus recommended (grade A) in patients who want a child; if the first resection is incomplete, a two-stage resection is recommended for fibroids less than 6 cm (grade C).

For submucosal fibroids, the use of bipolar energy (LE3) and antiadhesion gel (hyaluronic acid) makes it possible to reduce the risk of postoperative synechiae (LE2). An early hysteroscopy can check for the risk of these adhesions (LE4). On the other hand, only a few studies have examined the fertility benefits of these techniques (LE3). No data allow us to assess other techniques suggested for reducing the risk of adhesions (antiadhesion sheets, IUDs, silicone blades, estrogens, etc.).

In view of the initial results, it appears reasonable in the hysteroscopic resection of a submucosal fibroid tumor in a patient of child-bearing age desiring a child to use bipolar energy and antiadhesion gel and to verify the lack of adhesions hysteroscopically after one cycle (grade C). Larger studies are necessary to improve the grade of the recommendation for this approach to fertility.

4.1.2. For interstitial and subserosal fibroids

In the absence of symptoms, no data related to spontaneous pregnancies exist that would allow us to set a threshold for the number or size of fibroids above which the risk of infertility might increase.

A recent meta-analysis examined the effect of fibroids on pregnancy and the postpartum period and found a higher rate of obstetric complications (spontaneous abortion, pain, placentation disorders, IUGR, premature deliveries, abruptio placentae, breech presentations, labor dystocia, and postpartum hemorrhages) in patients with fibroids (LE2). Nonetheless, we cannot specify a threshold for the number or size of fibroids from which the risk of complications increased significantly. No study shows that myomectomy reduces this complication rate.

There is not yet enough evidence to argue that myomectomy (of an interstitial or subserosal fibroid) in the absence of infertility and symptoms would be useful for achieving pregnancy. It is nonetheless appropriate to inform the patient of the risks and complications inherent in fibroids that might affect fertility and pregnancy, and also of the complications for a future pregnancy that are inherent in this surgery (grade A).

No evidence supports recommending myomectomy during pregnancy in cases of obstetric disease, bleeding, necrobiosis or threatened preterm delivery attributable to fibroids (grade C).

A myomectomy during a cesarean delivery does not seem to be associated with any more morbidity than short-term abstention (LE3). Data on its long-term consequences are limited. There is no evidence to contraindicate myomectomy during a cesarean if it is either justified or necessary (previa) (grade C).

Finally, in the absence of data, a routine myomectomy after delivery is not indicated if a complication attributable to the fibroid occurred during pregnancy and the patient subsequently became asymptomatic again.

Symptomatic: Interstitial and subserosal myomectomies are feasible and reproducible by laparoscopy when the number of fibroids is low (<3) and their diameter less than 8 cm (CNGOF 2008) (LE2). Subsequent pregnancy rates are similar for myomectomies by laparotomy and laparoscopy (LE2). Myomectomy by laparoscopy takes longer than that by laparotomy (LE1); its utility and also the complications and the cost of morcellators must be considered (LE3). Blood loss is greater and the duration of hospitalization longer for myomectomy by laparotomy (LE1).

The principal risk of myomectomy is adhesions. Endoscopic techniques (laparoscopy and hysteroscopy) result in fewer adhesions (LE3). They nonetheless require trained operators. Inexperience is correlated with the risk of conversion to laparotomy (LE3). The use of antiadhesion barriers after myomectomy by laparotomy or laparoscopy reduces adhesion formation (LE1). The only study to have examined these barriers' clinical benefits for fertility found that the treatment increased the number of pregnancies (LE3). The risk of rupture after abdominal myomectomy seems low – less than 1% (LE4).

The laparoscopic approach is recommended for interstitial and subserosal myomectomies and for single fibroids of a diameter less than 8 cm (grade C). Above that, the technical problems and expected benefits must be assessed on a case-by-case basis. Laparotomic myomectomy is recommended for multiple fibroids (>3) or those measuring more than 9 cm (criteria from the literature) (grade C). The use of an antiadhesion barrier during myomectomy is recommended to prevent adhesions (grade A).

4.2. Role of myomectomy in infertility with and without assisted reproduction technologies

4.2.1. Without assisted reproduction

A submucosal fibroid has a negative effect on pregnancy rates in infertile patients seeking spontaneous conception (LE2). Hysteroscopic treatment of submucosal fibroids of types 0 and 1 increases the pregnancy rate in patients not using ART (LE1).

The presence of an intramural fibroid has a negative effect on the pregnancy rate in infertile patients with spontaneous conceptions (LE2). But the impact on fertility of the size and number of fibroids, as of any threshold values, cannot be defined precisely without an adequate evaluation; there are few studies, their evidence levels are low and their results discordant. Globally, surgical treatment of an asymptomatic intramural fibroid does not influence the subsequent fertility of infertile women in spontaneous conceptions. It appears that above a certain size (5–7 cm), myomectomy improves pregnancy rates (LE3), with identical efficacy for minilaparotomies and laparoscopies.

No study has reported the effect of subserosal fibroids on spontaneous fertility. Similarly, no study has specifically examined the benefits for fertility of surgery for subserosal fibroids. The data about surgical treatment – laparotomic or laparoscopic – of a subserosal fibroid, when it is the only factor of infertility found, have been extrapolated from work assessing this treatment for intramural fibroids. No conclusion can therefore be drawn. The data from the literature do not allow us to answer the question of whether surgical treatment of fibroids is indicated when they are associated with other factors of infertility.

4.2.2. With assisted reproduction technologies (ARTs)

Among infertile women using ART, fibroids from all sites combined have a negative effect on fertility indicators; rates of pregnancy, implantation, and live birth fall and the fetal loss rate increases (LE1). The same is true for submucosal fibroids alone (LE1). Similarly, intramural fibroids with and without intracavitary development have a negative effect on pregnancy, implantation, and live birth rates (LE1). The results of ART are less good when the size of the fibroid is greater than 4 cm (LE3). Subserosal fibroids have no negative effect on fertility indicators (LE4).

Surgical treatment by hysteroscopy of submucosal fibroids improved pregnancy rates for women using ART (LE2). Surgical treatment of intramural fibroids in ART patients does not improve the fertility indicators (LE2), and its impact on subserosal fibroids has not been evaluated.

It is recommended that submucosal fibroids of infertile women, whether or not they use ART, be treated by complete hysteroscopic resection to achieve pregnancy (grade B). In the absence of data about infertility, no recommendation about the use of bipolar energy or antiadhesion gels is possible. The insufficiency and heterogeneity of the data also make it impossible to issue a guideline about surgical treatment of interstitial fibroids that have no mass effect on the uterine cavity and of asymptomatic subserosal fibroids to achieve pregnancy in infertile women. It is therefore appropriate to assess the individual risk-benefit relation and inform the patient about the risks of pregnancy with fibroids and of surgery before reaching a decision about treatment.

4.3. Role of myomectomies in the perimenopausal period and afterwards

Because the natural course of fibroids in women older than 40 years is unpredictable (LE3), annual monitoring in a gynecologic examination is recommended. Although the literature is devoid of evidence about the need for routine ultrasound monitoring of fibroids, ultrasound remains the examination of choice for their diagnosis when symptoms appear and for monitoring changes when clinical modifications are observed (LE2). No data about completely expectant management are available. Expectant management is indicated for asymptomatic women (grade C). It is therefore appropriate to offer to treat only symptomatic fibroids, while providing women with information about the different possibilities and remaining respectful of the patient's opinion and desires (grade A). The appearance of new symptoms, the aggravation of old ones, or their persistence after nonsurgical treatment require reassessment and justify exploration by supplementary imaging (MRI or Doppler ultrasound) and endometrial biopsy (grade C).

For perimenopausal women with symptomatic submucosal fibroids or who wish to retain their fertility, hysteroscopic resection is the first-line treatment (grade B). Nonetheless, the patient must be informed of the risks of partial resection and of recurrence, as well as of the possibility of a second procedure (grade A).

For interstitial and subserosal fibroids in perimenopausal women, a laparoscopic approach is recommended for myomectomy of a single interstitial or subserosal fibroid of a diameter less than 8 cm (grade C). Above that, the technical difficulties and the expected benefits must be assessed on a case-by-case basis. Laparotomic myomectomy is recommended for multiple fibroids (>3) or those measuring more than 9 cm (criteria from the literature) (grade C). Women who want a myomectomy during the perimenopausal period must be informed of the low but possible risk of the need for further surgery (<15%) (grade A).

It is thus appropriate to inform women who choose myomectomy to preserve the potential for childbearing that their chances

of spontaneous pregnancy are low and their rate of spontaneous abortion is high and to warn them about the risks of pregnancy during the perimenopausal period (grade A). Myomectomy has not been shown to improve fertility in women older than 40 years.

In the absence of any desire for pregnancy among women who were informed of the alternatives to hysterectomy and of its risks, hysterectomy is the most effective treatment for symptomatic fibroids (LE1) and is associated with a high rate of patient satisfaction (LE2). When possible, the vaginal or laparoscopic approach should be preferred to laparotomy for hysterectomy (grade A). This intervention involves surgical risks about which the patient must be warned (grade A). Quality of life is globally improved by hysterectomy (LE2), as is sexuality, which improves somewhat (LE1) after both subtotal and total hysterectomy, by either laparotomy or laparoscopy. Vaginal hysterectomy has not been studied sufficiently, but is associated with more dyspareunia (LE4).

The problem of urinary continence is more complex: urgent and excessively frequent urination from mechanical (compressive) causes does improve; on the other hand, patients with hysterectomies are at twice as much risk of requiring surgical treatment for incontinence later on (LE3). Globally, few urinary modifications appear to be associated with hysterectomy, except in cases of preexisting disorders, which must be looked for during the preoperative history-taking (LE2).

When identical approaches are used, there does not appear to be a difference in complications between hysterectomy and myomectomy, including for transfusion rates (LE3).

4.3.1. After menopause

There are very few studies of the treatment of fibroids in menopausal women. The rarity of cancer of the associated endometrium or of sarcoma indicates that routine hysterectomies should not be performed for fibroids except in cases of Lynch syndrome. Nonetheless, after menopause, the size of fibroids diminishes, except in women receiving hormonal treatment; its appearance on ultrasound, an increase in size or the onset of symptoms all justify additional explorations, including a pelvic MRI and an endometrial biopsy (grade C). The existence of one of these three clinical or ultrasound signs and especially their combination justifies a surgical procedure rather than an alternative to hysterectomy, as morcellation must be avoided in this situation (grade C).

Beyond this particularity, the guidelines for surgical treatment are identical to those for the management of symptomatic fibroids in perimenopausal women.

Hormone replacement treatment is not contraindicated for women with fibroids but the patient must be informed of the risk of changes under treatment and of the need to consult if symptoms occur (grade C).

5. Question 3: alternatives to conventional surgery (total hysterectomy or myomectomy)

5.1. Role of uterine artery embolization [25–32]

In the first place, generally, not enough data are available to enable a guideline to be based on the number or size of fibroids that it is possible to embolize. On the other hand, neither a single submucosal intracavitary fibroid (types 0 and 1) nor a single subserosal pedunculated fibroid (grade C) should be treated by embolization because of the risk of complications.

Non-spherical polyvinyl alcohol (PVA) particles are associated with a higher rate of microcatheter occlusion than are tris-acryl microspheres. These particles do not differ for post-embolization pain intensity or analgesic dose. Similarly, non-spherical PVA particles do not differ from the tris-acryl microspheres (>500 μm) in terms of clinical efficacy, reduction of uterine volume, or complication rate. The clinical efficacy of the PVA microspheres (Contour SE and Bead Block) is lower and they have a lower rate of fibroid devascularization, as assessed by MRI, than do the tris-acryl microspheres (Embosphere) (LE2). Consequently, it is recommended that particles greater than 500 μm be used to embolize uterine fibroids (grade B).

Uterine artery embolization with non-spherical PVA particles or with tris-acryl microspheres larger than 500 μm provides efficacious short-term treatment of heavy menstrual bleeding, compression symptoms and pelvic pain in 90% of cases (LE1).

In the longer term, their efficacy for heavy menstrual bleeding and compression symptoms is 75% at 5–7 years (LE1). The reduction of uterine volume at 6 months varies between 30 and 60%, and the volume reduction of the dominant fibroid between 50 and 80% at 6 months (LE1). The rate of complications during hospitalization is assessed at 3%. The rate of hysterectomies due to embolization complications is less than 2% at 3 months. The rate of permanent amenorrhea after embolization is less than 5% among women aged younger than 45 years. Embolization has no effect on the hormonal functioning of women younger than 45 years if their hormone studies are normal. The rate of secondary hysterectomy for clinical inefficacy or recurrence is 13–28% at 5 years (LE1), depending on the study.

It is therefore possible to conclude that uterine artery embolization is an effective treatment with a low morbidity rate and thus a treatment option for symptomatic fibroids in women who do not want to become pregnant (grade A).

The efficacies of embolization and of hysterectomy by laparotomy for compression symptoms and pelvic pain do not differ at 12 or 24 months. There is no difference in quality of life between women who had embolization and those who had hysterectomy by laparotomy at 12 months, 24 months or 5 years; similarly, the satisfaction rate for embolization and hysterectomy by laparotomy does not differ at 24 months (LE1).

The rate of minor intraoperative complications is higher for embolization than for laparotomic hysterectomy, but the major intraoperative complication rate is higher for the latter than the former. In the first 24 h after treatment, pain assessed by a visual analogic scale is more intense after hysterectomy by laparotomy than after embolization.

The rate of major complications at 6 weeks is higher after hysterectomy by laparotomy than after embolization. The major complication rate at 1 year, however, does not differ for these two techniques (LE1). Revision surgery, however, is more frequent after embolization than after hysterectomy in the randomized trials: secondary hysterectomy is necessary after embolization in 13–24% of cases at 2 years and up to 28% of cases at 5 years (LE1).

The duration of hospitalization, convalescence and sick-leave is shorter after embolization than after hysterectomy by laparotomy, and the cost of embolization is less at 12 months and at 24 months, even taking into account the cost of the follow-up imaging and revision surgery (LE1).

Patients must be informed that uterine artery embolization is an alternative to hysterectomy by laparotomy for the treatment of one or more symptomatic fibroids, if they do not want to conceive (grade A). In the absence of a study comparing uterine artery embolization with vaginal or laparoscopic hysterectomy, no recommendation can be made. It is desirable to inform the patient of this option in all cases where vaginal or laparoscopic hysterectomy will be suggested.

At 6–26 months after treatment, efficacy for either bleeding or compression symptoms does not differ between women who had embolizations and those who had myomectomies (LE2), nor does the reduction of uterine volume differ. Similarly, the two

procedures are associated with the same quality of life at 6 months (LE3).

The perioperative and 30-day complication rates do not differ (LE2), but the 6-month complication rate is higher after myomectomy (laparoscopic or laparotomic) than after embolization (LE3). Nonetheless the rate of revision surgery is higher after embolization than after myomectomy (LE2).

The durations of hospitalization and convalescence (LE2) as well as of sick-leave (LE3) are shorter after embolization than after either type of myomectomy.

Finally embolization is associated with more frequent elevation of FSH levels than myomectomy. The conception rate after myomectomy is higher than after embolization, as is the number of term pregnancies; the miscarriage rate, however, is lower (LE3).

There is no significant difference between embolization and myomectomy for rates of preterm delivery, cesarean delivery, postpartum hemorrhage, preeclampsia, or in utero growth restriction (LE2). Patients must be informed that uterine artery embolization is an alternative to myomectomy (by laparoscopy or laparotomy) for the treatment of non-submucosal symptomatic fibroids (type 0 or 1) for women who do not want to retain their fertility (grade A).

Uterine artery embolization is not a first-line treatment for women who want to become pregnant (grade C). Patients must be informed of the risks in case they decide they want to become pregnant after embolization (grade A).

Uterine artery embolization before myomectomy (preoperative or combined technique) significantly reduces intraoperative bleeding (LE3) and can be considered on a case-by-case basis (grade C).

5.2. Role of destructive alternatives to surgical treatment for fibroids, other than embolization

5.2.1. Myolysis or destruction of fibroids [33–39]

The Nd:YAG laser has proved efficacious, but the cost of the equipment, the fragility of the fibers and the risk of postoperative adhesions have limited its development (LE4).

Myolyses with bipolar needles or microwave are techniques of limited use today, appropriate only in research settings.

Radiofrequency myolysis appears to be an efficacious and minimally invasive technique, but studies of larger cohorts are necessary (LE4). Radiofrequency myolysis is an invasive alternative when it is performed by laparoscopy and less aggressive when it can be performed under ultrasound guidance with a vaginal approach. Nonetheless, the existing series demonstrate only the feasibility of this technique; they include several hundred patients and no comparative trials.

Cryomyolysis remains an experimental procedure; the data currently available in the literature are insufficient to establish its efficacy or its safety (LE4).

MRI- or ultrasound-guided focused ultrasound treatment is a new possibility, and current results are encouraging, after the learning curve. Rigorous selection of patients is essential with treatment of a single fibroid or two at the most, anterior, between 5 and 12 cm, with a T2-weighted hypointense signal T2 on MRI; approximately 10% of fibroids are accessible to this technique to obtain devascularization greater than 45%, which is correlated with intermediate-term symptom relief in the order of 60–70% (LE3). On the other hand, the reduction of fibroid volume seems less substantial (15–40%) than with the other techniques (LE4). None of the current techniques can be recommended for myolysis; the technique that is most advanced, least aggressive and monitored most effectively seems to be focused ultrasound. Clinical research into these techniques must continue, with trials comparing them to surgery or uterine artery embolization, to obtain an evidence level sufficient to justify a recommendation. Patients treated with these techniques must be included in research protocols.

As of today, no publication provides evidence to justify either allowing or proscribing myolysis in women who wish to become pregnant (grade C).

5.2.2. Laparoscopic ligation of the uterine arteries

Laparoscopic ligation of the uterine arteries is better tolerated but less efficacious than embolization (LE2), because for the same indications (but with limited accessibility in terms of uterine volume) it produces results that are similar at 6 months (reduction of volume by 30–50% and of symptoms by 50–80%) but less durable over time (LE2). Its efficacy combined with myomectomy has been studied relatively little, but it diminishes bleeding significantly (LE2). Isolated laparoscopic ligation of the uterine arteries is a possible alternative but is less efficacious in the long-term than uterine artery embolization (grade B).

5.3. Role of alternatives to hysteroscopic myomectomy for the treatment of fibroids [40–44]

Techniques of endometrial reduction of submucosal fibroids are efficacious (measured by the Higham score and the hemoglobin level) separately or combined with hysteroscopic resection in women who do not wish to preserve their fertility (LE2).

The second-generation techniques of endometrial reduction (thermocoagulation, thermal ablation, radiofrequency or microwave endometrial ablation) involve shorter surgical procedures and lower complication rates than those of the first generation (hysteroscopic endometrial resection, endometrial ablation by laser Nd:YAG or rollerball). These techniques are particularly interesting for patients at high risk during anesthetics or surgery (LE1). Moreover, it appears that endometrial ablation concomitant with destruction of submucosal fibroids is more efficacious for controlling bleeding than myomectomy alone (LE4).

Few subsequent pregnancies have been observed: of the order of 0.7% after hysteroscopic resection, and up to approximately 5% for the second-generation techniques. The outcomes described have mainly been elective abortions, miscarriages and ectopic pregnancies. Moreover these pregnancies present particular risks for fetus and mother. The early abortions are complicated, more frequently than in the general population, by their failure to be evacuated due to stenoses or cervical synechiae, and they can even require hysterectomy (LE4). For pregnancies continuing beyond 20 weeks, high rates of cesarean deliveries, preterm births, abnormal placental insertion and premature rupture of the membranes are found. There are also more perinatal deaths and secondary hysterectomies. Finally, two cases of uterine rupture have been described, including one followed by maternal death due to massive hemorrhage (LE4).

Finally, the cost-efficiency relations of these types of fibroid management have yet to be assessed.

It is thus possible to use second-generation techniques of endometrial ablation to treat the menometrorrhagias associated with submucosal fibroids in women whose families are complete (grade B). On the other hand, the pregnancies that might occur after these conservative treatments present substantial risks (LE4), and the patient must be informed beforehand (grade A). Effective contraception is advised (grade C). It is also possible to perform hysteroscopic sterilization by Essure® during the same procedure as thermal ablation by Thermachoice® or bipolar resection (the only studies thus far published) (LE4).

Acupuncture has no role in the therapeutic armamentarium for the treatment of fibroids, in view of the lack of scientific proof of its efficacy.

6. Question 4: role of subtotal compared with total hysterectomy for fibroids. [45–49]

Preservation of the cervix during a laparotomic hysterectomy shortens the operative time by approximately 17% (LE1). It saves no time when the hysterectomy is laparoscopic (LE2), probably because of uterine morcellation. Preservation of the cervix diminishes the blood loss from laparotomy without influencing the intraoperative transfusion rate (LE1), but blood loss is similar for the two techniques (LE2).

The preservation of the cervix during a hysterectomy by laparotomy reduces the onset of postoperative febrile episodes (LE1), while the rate of minor and major complications during laparoscopy is identical for total and subtotal procedures (LE2). It does not affect the duration of postoperative convalescence after laparotomy (LE1); the controversial results of studies using laparoscopy do not allow any definitive conclusion (LE4).

Finally, no prospective randomized trials of large numbers of women have compared ureteral morbidity in total and subtotal hysterectomies. Nonetheless laparoscopy seems to increase the ureteral risk of all types of hysterectomy, either total or subtotal, and there does not seem to have been a difference between total and subtotal, both being highly linked to a learning curve (LE2). Laparoscopic subtotal hysterectomy, on the other hand, seems to diminish the bladder risk compared with the incidence of bladder wounds for total hysterectomy, but no randomized trial has been conducted (LE3).

Subtotal hysterectomy is an alternative to total hysterectomy for fibroids (grade B), for the number of complications is reduced in laparotomies and identical in laparoscopic procedures. The risk of cancer of the cervical stump is approximately 0.05% after three normal PAP smears (LE2). If preservation of the cervix is considered, the patient must be informed that it is necessary to continue regular PAP smears for screening (grade A). The relative risk of cervical cancer triples in women with a history of cervical dysplasia (LE1). Nonetheless, there are no studies of cohorts of women with a history of dysplasia and followed after total and subtotal hysterectomies.

Light and untroublesome cyclical bleeding is observed in up to 20% of women who have had a subtotal hysterectomy. Conization of the endocervix during subtotal hysterectomy appears to reduce the incidence of cyclical bleeding from 10% to 1.4% (LE2). The inexperience of the operator increases the risk of revision surgery for this cause (LE4).

In terms of long-term functional aspects, cervical preservation, by either laparotomy or laparoscopy, does not appear to affect long-term functional aspects: not the quality of sexual relations in the intermediate term (LE1), or quality of life (LE1) except for improvement of body image, or the onset of urinary, gastrointestinal or pelvic disorders (LE1). Performance of a subtotal rather than a total hysterectomy to avoid functional, sexual or pelvic disorders is not justified (grade A).

7. Conclusion

These guidelines (full texts with all Refs. [51–61]) for the therapeutic management of fibroids update and supplement the guidelines issued in 2000 and 2008. They consider the literature through September 2011, sometimes very limited especially in terms of determining the threshold size or number of fibroids. They are designed for women whose fibroids have been diagnosed with certainty and mapped accurately with the necessary and sufficient imaging tools (pelvic and transvaginal ultrasound in two or three dimensions with Doppler, contrast or hysterosonography if necessary; second-line MRI with T1- and T2-weighted views and injection of gadolinium). They must be accompanied by comprehensive management of the patient, treating the fibroids, symptoms and consequences (anemia, physical and psychological effects). Finally, they are intended to serve as the foundation of clinical practice today, to be presented and discussed with patients, while respecting their desires and choices within the limits of medical ethics and reason.

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