EXTRACT from the Gynaecology and Obstetrics Update

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Levels of evidence and grades of recommendations according to the HAS (French National Authority for Health) cited by some authors

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<th>Level of scientific evidence provided by literature (therapeutic studies)</th>
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<td><strong>Level 1 (LP1)</strong>  &lt;br&gt; High-power comparative randomized trials  &lt;br&gt; Meta-analysis of comparative randomized trials  &lt;br&gt; Analysis of decision based on well-conducted studies</td>
<td>A  &lt;br&gt; Established scientific evidence</td>
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<td><strong>Level 2 (LP2)</strong>  &lt;br&gt; Low-power comparative randomized trials  &lt;br&gt; Non-randomized, well-conducted comparative studies  &lt;br&gt; Cohort studies</td>
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<td><strong>Level 3 (LP3)</strong>  &lt;br&gt; Case-control studies</td>
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Clinical Practice Guidelines

Update on the management of myoma

Drawn up by the French National College of Gynaecologists and Obstetricians

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INTRODUCTION

Myoma (fibroids) are the most common disorder in women. They are responsible for meno-metrorrhagia (primary cause for women between 40 and 50 consulting a doctor) and pelvic pain, and are the primary cause of hysterectomy in France.

As its previous guidelines date back to 1999, the CNGOF has decided to update these guidelines, taking into account the diagnostic and technical advances of the last 10 years.

Drafting these guidelines involved setting up a working group to define the questions, selecting a team to answer the questions, and establishing levels of evidence and grades for each recommendation so that they can be used by French-speaking doctors when practicing evidence-based medicine.

All professionals must be made to understand that it is important that these guidelines be followed since they constitute current best practice.

This new version of the guidelines attempts to re-define the role of the medical treatment of fibroids, in terms of their symptoms, to re-discuss the role of fibroids in fertility or infertility, to define the role of new alternatives to surgery in the treatment of fibroids by relating them to new XXIst century problems (the desire to keep the uterus capable of child-bearing for as long as possible, linked to the desire of patients and possibilities for new techniques of assisted reproduction), and to re-discuss, in the light of new surgical techniques, the actual role of each surgical indication.

The premise on which this study was based was that only symptomatic fibroids justify a therapeutic approach.

Methodology

The sponsor (CNGOF) commissioned a scientific committee whose responsibility it was to select expert writers, define the questions and draft the summary of recommendations that originated from these studies. The questions related to the medical treatment of symptomatic myoma, the indications for myomectomy, the alternatives to surgery and the role of subtotal hysterectomy. The experts carried out an analysis of the existing scientific literature on the subject to answer the questions posed. For
each question posed, the summary of valid scientific data was allocated a level of evidence, established as a function of the quality of available data using the reading grid defined by the HAS (LP1: High-power comparative randomized trials, meta-analysis of comparative randomized trials; LP2: Low-power comparative randomized trials, non-randomized, well-conducted studies, cohort studies; LP3: case-control studies; LP4: comparative studies with significant bias, retrospective studies, transversal studies, case series). The summary of recommendations was drawn up by the scientific committee based on the responses provided by the expert writers. Each of the practice guidelines was allocated a grade, based not only on the level of evidence, but also on the expected clinical benefit and the ethical issues. Grade A represents established scientific evidence; grade B represents scientific presumption; grade C relies on a low level of evidence, generally based on LP3 or LP4. In the absence of conclusive scientific evidence, some practices however were still recommended if all working group members agreed, but these were not graded. The number of such professional agreements was restricted to an absolute minimum.

The entire text plus the summary of recommendations was proof-read by external readers, practitioners from the various specialities concerned, and from various backgrounds (public, private, university, non-university), and then amendments were incorporated.

QUESTION 1: MEDICAL TREATMENT OF MYOMA-RELATED SYMPTOMS

1.1 General context

There is no currently validated medical treatment that is capable of making myoma disappear (LP1), it follows from this: that in the case of asymptomatic myoma, there is no need to consider medical treatment (grade A); - that in the presence of symptomatic myoma (pain or bleeding); - the sole objective of medical treatment is to treat the symptoms associated with the myoma (grade C); - however, symptomatic submucosal myomas should in the first instance be dealt with surgically and not exclusively by medical treatment (grade B).

1.2 Available medical treatments

1.2.1 Progestogens

Prescribing a progestogen treatment aims to reduce the menometrorrhagia by decreasing the endometrial hyperplasia associated with myomas (LP2); the verbally-reported benefit is 25-50% whether in the second part of the cycle or as a contraceptive for 21 days and there is no continuous data. The benefit of the levonorgestrel-releasing intrauterine device on the symptoms linked to myomas (not including submucosal location) was established based on the reduction in bleeding and recovery of haemoglobin levels (LP2). [CNGOF 2008 Guidelines].

Prescribing a progestogen treatment does not constitute a treatment for myomas, but can be proposed as a treatment for the menometrorrhagia associated with the myomas as a short-term to medium-term solution (grade C). Progestogen treatment administered by endo-uterine route (levonorgestrel-releasing IUD) for menometrorrhagia linked to fibroids has been validated and can be recommended (grade B).

1.2.2 Anti-fibrinolytics

Menorrhagia linked to uterine myomas is caused by local fibrinolysis. Tranexamic acid is effective in the treatment of menorrhagia linked to myomas (LP2).

Prescription of tranexamic acid can be proposed to treat menorrhagia associated with myomas (grade B).

1.2.3 Non-steroidal anti-inflammatories

NSAIDS can reduce menorrhagia but are less effective than tranexamic acid, Danatrol or levonorgestrel-releasing IUD (LP1).

They are effective against pain linked to the aseptic necrobiosis of a myoma (LP2).

Prescription of an NSAID treatment can be proposed to treat the symptoms associated with myomas (grade B).

1.2.4 GnRH analogues

These are used in a pre-operative context and can only be administered occasionally because of their side effects. They enable a reduction in bleeding and a recovery of the haemoglobin to a level that is similar to the pre-operative level (LP1). A 2-3 month course of treatment, which is in line with the marketing authorization, seems to be adequate (LP1).
Addition of tibilone to GnRH agonists does not adversely impact the improvement of myoma-related symptoms and enables an identical reduction in the size of myomas (LP1). It appears that the side effects conventionally encountered with the GnRH agonists are limited by the addition of tibilone (LP1).

Add-back therapy using oestrogens reduces the size of the myomas, but to a lesser extent than agonists alone (NP3). The addition of raloxifen does not adversely impact the benefits linked to agonist treatment but neither does it prevent hot flushes (LP2).

Leuprolrelin and triptorelin are pre-operative treatments for uterine myomas associated with anaemia (Hg < 8 g/dl), or when it is necessary to reduce the size of the myoma to facilitate or modify the surgical technique: endoscopic surgery, transvaginal surgery (grade A). Duration of pre-operative treatment is limited to 3 months. There is no indication for “add-back therapy” with oestrogens or raloxifen, however addition of tibilone is possible (grade B).

1.2.5 GnRH antagonists

GnRH antagonists when administered at effective doses reduce the volume of the uterus without reducing the volume of myomas at day 28. In addition, although they do not improve the haemoglobin level at day 28, their administration reduces menorrhagia/dysmenorrhoea (LP2). They are not considered as a treatment for myomas.

Use of GnRH antagonists is not contra-indicated in medically-assisted reproduction in the presence of a uterine myoma (grade C).

1.2.6 Danazol

Danazol is effective short-term (less than 3 months) in reducing symptoms linked to uterine myomas but no studies have evaluated its long-term efficacy (over 6 months). Danazol appears to be less effective than GnRH agonists and causes more side effects (LP2).

The use of danazol in myomatous disease is not recommended owing to the side effects encountered and the fact that it is only effective for a short time (grade C).

1.2.7 Aromatase inhibitors

Aromatase inhibitors: letrozole, anastrozole and exemestane.

Aromatase inhibitors have been proposed. These drugs are rapidly effective on symptoms and reduce the size of the myoma (LP1).

Apart from in research, aromatase inhibitors are not indicated to date in the treatment of myoma.

1.2.8 Anti-progesterone and PRMs

Administration of mefipristone reduces the size of myomas and improves the symptoms associated with them (LP1). However, endometrial hyperplasia may develop and therefore caution is advised. The 5 mg/day dosage gives similar results to the 10 mg/day dosage (LP1) and may reduce the risk of endometrial hyperplasia (LP2).

Progestrone receptor modulators (PRMs – CP8947, onapristone, CDB 2914, ulipristal, asoprisnil) are being assessed in the treatment of myomas, phase IIb trials have shown good efficacy after 3 – 6 months’ administration in reducing the symptoms and the anaemia linked to bleeding from the myomas, but also in reducing the size of the myomas (LP2). Amenorrhoea appears to be common.

Ulipristal is completing phase III trials in this indication.

In the absence of a marketing authorization, mefipristone or PRMs are not indicated to date outside clinical studies in the treatment of uterine myomas.

1.3 Special cases

1.3.1 Myoma and contraception (not including IUD)

There is currently no evidence in the literature to suggest that oral contraceptives favour the development or growth of uterine myomas, whether conventional oestrogen-progesterone oral contraceptives, second or third-generation oral contraceptives (20 – 30 µg ethinyl-oestradiol dose), or normal doses of progestosterone contraceptives (LP3).

Oestrogen-progesterone contraceptives, progestrone contraceptives or the morning-after pill are not contra-indicated in myomas (grade C). On the other hand, these contraceptives are not a treatment for myomas (grade C).

1.3.2 Myoma and hormonal treatment for menopause (HRT)

Asymptomatic myomas do not constitute a contra-indication for hormone replacement therapy (grade C) as there is no evidence that HRT causes myomas to grow. However, HRT does increase the risk of menorrhagia in the case of submucosal myoma (LP3).

1.3.3 Myoma and intrauterine devices

Because of the increased risk of haemorrhagic complications and of expulsion, submucosal myomas are a relative contra-indication to intrauterine devices (grade C).
The levonorgestrel-releasing intrauterine device significantly reduces menorrhagia linked to myomas (LP2) (not including submucosal myomas). Therefore it is recommended in this indication (grade B).

In conclusion, before prescribing any medical treatment for myomas, a personalized benefit-risk assessment must be carried out on these patients, taking into account the side effects and secondary complications of these drug treatments.

QUESTION 2: MYOMECTOMY

Patients who undergo (poly)myomectomy surgery must be informed of the risk of their symptoms persisting, and of the possibility of a recurrence of the myoma or myomas, which could require re-intervention (grade A). In the case of myomectomy by laparotomy or coelioscopy, and if the patient is likely to become pregnant later on, patients must also be informed of the risk of uterine rupture during a future pregnancy. The route of delivery will be determined by the obstetric team taking into account the data in the surgical report and the outcome of intervention.

There are no data in the literature concerning the management of asymptomatic myomas nor the threshold size limit of such management. However, in the case of myomas measuring more than 10 cm prior to the menopause, surgery and alternative treatments for fibroids will definitely be more aggressive and risky the greater the uterine volume (LP3). Regular monitoring should be carried out to evaluate the growth progression of myomas over 10 cm prior to the menopause.

2.1 Role of myomectomies in the event of spontaneous conception or a woman who wishes to remain fertile

(The patient is not fertile but wishes to become pregnant, or she does not wish to become pregnant but would like to leave her options open).

A link has been observed between infertility and myoma (LP2), but the role of myomas in infertility has yet to be established. The link between myoma and infertility can be explained, at least in part, by the age of women at the time of conception. In fact the incidence of myomas and infertility increases with age.

2.1.1 Concerning submucosal myomas

If they are symptomatic: the complete hysteroscopic resection of submucosal myomas effectively treats menorrhagia in women with a normal-sized uterus comprising a single submucosal myoma measuring less than 4 cm in a predominantly intra-cavity location (LP3). The results in other conditions are not as good, but can be improved by preparation with GnRH agonists, or by iterative resection (LP4). The 2008 recommendation for intra-cavity myomas is preserved: complete hysteroscopic resection as first-line treatment in symptomatic and submucosal myomas, type 0, 1 (grade B) and 2 (grade C) up to 4 cm (grade C); this is also possible in myomas measuring 4-6 cm. In the case of incomplete resection, a two-stage operation is recommended for submucosal myomas. The thickness of the residual posterior myometrial wall in front of the serous membrane must be measured; in order to avoid complications a limit of 5 mm (the most common criterion used in the literature) must be adhered to. The reported risk of rupture of the uterus during pregnancy following myomectomy by hysteroscopy is practically zero (LP4).

If they are asymptomatic, and therefore discovered on a scan, treatment by hysteroscopy of submucosal myomas which deform the uterine cavity will improve fertility (LP1). Complete hysteroscopic resection of submucosal myomas which are asymptomatic but which deform the cavity is recommended (grade A) in patients who wish to become pregnant; in the case of incomplete resection, a two-stage resection is recommended for myomas measuring less than 6 cm (grade C).

In the case of submucosal myomas, the use of bipolar energy (LP1) and anti-adhesive hyaluronic acid-based gel reduces the risk of post-operative synechiae (adhesions) (LP2). An early follow-up hysteroscopy will screen for post-operative synechiae (LP4). However, there are few studies on the benefit on fertility of bipolar energy, anti-adhesive gel or post-operative hysteroscopic checks (LP3). There are no data relating to the other techniques proposed for reducing the risk of synechia (anti-adhesive patches, IUDs, silicone mesh, oestrogens etc.).

In the case of resection by hysteroscopy of a submucosal fibroid in a patient who wishes to become pregnant or is of child-bearing age, and in view of initial results from the literature, it appears reasonable to use bipolar energy or anti-adhesive gel, and to carry out a hysteroscopic check-up after one cycle to prevent or screen for synechiae (grade C). In addition, several studies would need to be conducted to increase the grade of recommendation for this fertility-related attribute.
2.1.2 Concerning interstitial and subserosal myomas

In the absence of symptoms: there are no available data on spontaneous reproduction which could help to establish a number or a threshold of size of myoma beyond which the risk of infertility increases.

Concerning the impact of myomas on pregnancy and post-partum, a recent meta-analysis discovered an increased level of obstetric complications (spontaneous miscarriage, pain, placental disorders, intrauterine growth retardation, premature labour, placental abruption, dystocic presentations, post-partum haemorrhage) in the case of myomas (LP2). However, it is not possible to state a threshold number or size of myoma beyond which the risk of complications significantly increases. There are no studies that demonstrate that myomectomy reduces this level of complications.

There is insufficient evidence to date to indicate myomectomy (interstitial and subserosal myoma) in the absence of infertility and symptoms with the aim of achieving pregnancy. However, it would be advisable to inform the patient of the inherent risks and complications of myomas in relation to fertility and pregnancy, but also of the inherent complications of surgery on a future pregnancy (grade A).

In the event of an obstetric disorder, bleeding, necrobiosis and the threat of premature labour, attributed to the presence of a myoma, there is no evidence to recommend myomectomy during pregnancy (grade C).

Performing a myomectomy during a Caesarian is no more clinically difficult than doing the myomectomy at a later date (LP3). Data relating to the long-term consequences are limited. There is no evidence to contra-indicate myomectomy during a Caesarian if the myomectomy is justified or necessary (praecox) (grade C).

Finally, in the absence of data, there is no evidence to support performing systematic myomectomy after labour where there have been complications attributable to myoma during pregnancy and the patient has become asymptomatic again.

With symptoms: interstitial and subserosal myomectomies are feasible and reproducible by coelioscopy when the myomas are few in number (<3) with a diameter of less than 8 cm (2008 Clinical Practice Guidelines) (LP1). The rate of pregnancies in the case of myomectomies by laparotomy and coelioscopy are similar (LP2). Surgery time for myomectomy by coelioscopy is greater than for myomectomy by laparotomy (LP1); morcellators constitute an advance, but the complications and the cost of must also be taken into account (LP3). Blood loss is greater and the time spent in hospital longer in the case of myomectomy by laparotomy (LP1). The risk of adhesions is the main risk associated with myomectomy.

Endoscopic techniques (coelioscopy, hysteroscopy) are less likely to cause adhesions (LP3). However, they require trained operators. Inexperience is correlated with the risk of laparoconversion (LP3). The use of anti-adhesive barriers following myomectomy by laparotomy and by laparoscopy reduces the development of adhesions (LP1). The clinical benefit on fertility of anti-adhesive barriers is not well documented (one study) but favours an increase in the number of pregnancies (LP3). The risk of rupture following myomectomy by abdominal route appears to be low (less than 1 %) (LP4).

The coelioscopic route is recommended for interstitial and subserosal myomectomies, for single myomas of less than 8 cm in diameter (grade C). Moreover, the technical difficulties and the expected benefit must also be assessed on a case-by-case basis. Myomectomy by laparotomy is recommended for multiple myomas (>3) or myomas measuring more than 9 cm (criteria used in the literature) (grade C). The use of an anti-adhesive barrier during myomectomy is recommended to prevent adhesions (grade A).

2.2 Role of myomectomy in the case of infertility with and without medically-assisted reproduction

2.2.1 Without medically-assisted reproduction

The presence of a submucosal myoma has a deleterious effect on the rate of pregnancies by spontaneous conception in an infertile patient (LP2). Hysteroscopic treatment of type 0 and type I submucosal myomas increases the rate of pregnancy without medically-assisted reproduction (LP1).

The presence of an intramural myoma has a deleterious effect on the rate of pregnancies by spontaneous conception in an infertile patient (LP2). But the impact on fertility of the size and number of myomas, just as the threshold values, cannot be precisely defined in the absence of an adequate analysis (few studies, low levels of evidence, conflicting results). Surgical treatment for an asymptomatic intramural myoma does not generally affect the subsequent fertility of infertile women by spontaneous conception; it appears that above a certain size (5-7 cm), myomectomy improves the rate of pregnancy (LP3), with identical efficacy to mini-laparotomy and coelioscopy. No studies have been conducted on the impact of subserosal fibroma on spontaneous fertility. There are also no specific studies on the benefit in terms of fertility of subserosal myoma surgery. The data on surgical treatment, either by laparotomy or coelioscopy, of subserosal
myoma, when it is the only infertility factor found, are extrapolated from studies evaluating this treatment for intramural myomas. However, no conclusion can be drawn. Data from the literature do not answer the question of whether surgical treatment should be indicated for myomas when other factors of infertility are involved.

2.2.2 With medically-assisted reproduction

Within the context of the management of an infertile patient undergoing assisted reproduction, all myomas, regardless of location, have a harmful effect on fertility parameters, reducing the rate of pregnancy, the rate of implantation, the rate of live births and increasing the rate of foetal loss (LP1). Submucosal myomas have a harmful effect on fertility parameters, reducing the rate of pregnancy, the rate of implantation, the rate of live births and increasing the rate of foetal loss (LP1). Intramural myomas with and without intracavity protrusion have a harmful effect on fertility parameters, reducing the rate of pregnancy, the rate of implantation and the rate of live births (LP1). The results of medically-assisted reproduction are not as good if the myoma measures more than 4 cm (LP3). Subserosal myoma do not have a harmful effect on fertility parameters (LP4).

Within the context of the management of an infertile patient undergoing medically-assisted reproduction, surgical treatment by hysteroscopy of a submucosal myoma improves the rate of pregnancy (LP2). Surgical treatment of an intramural myoma in an infertile patient undergoing medically-assisted reproduction does not improve fertility parameters (LP2). The impact of surgical treatment of a subserosal myoma in an infertile patient undergoing medically-assisted reproduction has not been established.

In the case of infertility, whether the patient is undergoing assisted reproduction or not, it is recommended that submucosal myomas are treated by total hysteroscopic resection with the aim of achieving pregnancy (grade B). In the absence of data on infertility, it is not possible to make any recommendations on the use of bipolar energy or anti-adhesive gels. Since the data are inadequate and diverse, it is not possible to make any recommendations on the benefit of surgical treatment for interstitial myomas which have no space-occupying effect in the cavity, or asymptomatic subserosal myomas with the aim of achieving pregnancy in an infertile woman. Therefore it is a good idea to evaluate the individual risk-benefit profile and to inform the patient of the risks of pregnancy with myoma, and the risks of surgery, before establishing a therapeutic indication.

2.3 Role of myomectomy during and after the menopause

Above 40 years of age, since the natural evolution of myomas cannot be predicted (LP3), it is recommended that women undergo an annual gynaecological examination to monitor the situation. Although there is no evidence in the literature to support systematic ultrasound monitoring of myomas, ultrasound remains the examination of choice in diagnosing and controlling the evolution of myomas before symptoms or clinical changes appear (LP2). There are no data on total abstinence from treatment. Abstinence from treatment is indicated in an asymptomatic patient (grade C). Therefore it is advisable only to propose treatment of symptomatic myomas – the patient should be informed of the various alternatives and the opinions and wishes of the patient should be respected (grade A). The development of new symptoms or worsening of symptoms, or the persistence of symptoms after non-surgical treatment, will require a re-evaluation and justify an additional scan investigation (MRI or Doppler ultrasound) and endometrial biopsy (grade C).

The treatment of choice in women in peri-menopause presenting with a symptomatic submucosal myoma or who wish to preserve their child-bearing capacity, is hysteroscopic resection (grade B). However, the patient must be informed of the risk of partial resection, of recurrence and of the possibility of a second intervention (grade A).

The coelioscopy route is recommended in peri-menopausal women with interstitial and subserosal myomas to remove myomas measuring less than 8 cm (grade C). The technical difficulties and the expected benefit must also be evaluated on a case-by-case basis. Myomectomy by laparotomy is recommended for multiple myomas (> 3) or myomas measuring over 9 cm (criteria used in the literature) (grade C).

Peri-menopausal patients who would like a myomectomy must be informed of the small but possible risk of re-intervention (< 15%) (grade A).

Therefore patients who opt for myomectomy to preserve potential fertility should be informed that their chances of spontaneous pregnancy are low and the rate of spontaneous miscarriage is increased; they should also be warned of the risks of pregnancy during the peri-menopause (grade A). The benefit of myomectomy on fertility beyond the age of 40 has not been established.

In the absence of any desire to become pregnant, the most effective treatment for symptomatic myomas in women who have been informed of the alternatives and the risks of intervention, is hysterectomy (LP1), which is associated with a high level of satisfaction (LP2). Where possible, the vaginal route or coelioscopy is preferred over laparotomy when performing hysterectomy.
This intervention involves surgery-related risks which the patient must be warned about (grade A). Quality-of-life is generally improved by hysterectomy (LP2), as is sex-life which usually improves (LP1), whether following subtotal or total hysterectomy, by laparotomy or coelioscopy. The vaginal route has not been evaluated very much and there is more dyspareunia (painful intercourse) (LP4). The problem of urinary continence is more complex: urgency and frequency improves if mechanical (compressive); on the other hand, patients who have undergone hysterectomy have a two-fold greater risk of having to subsequently undergo surgical treatment for incontinence (LP3). Overall it appears that few urinary changes are linked to hysterectomy in the absence of pre-existing problems; the patient should be asked about these during the pre-operative consultation (LP2).

If the access route is identical, there does not appear to be any difference in terms of complications between hysterectomy and myomectomy including risk of transfusion (LP3).

**After the menopause**

There have not been many studies on the treatment of fibroids in postmenopausal patients. As endometrial cancer and sarcoma are rare, hysterectomy should not be performed systematically in the presence of myomas except in the case of Lynch syndrome. However, fibroids decrease in size after the menopause. In the absence of hormone treatment, the appearance of a myoma on ultrasound, an increase in its size or the appearance of symptoms justifies a request for additional investigations by pelvic MRI and endometrial biopsy (grade C).

The presence of one of these three clinical signs, or a combination of signs, justify performing a surgical procedure rather than any alternative to hysterectomy; morcellation should be avoided in this circumstance (grade C).

Apart from these guidelines, the therapeutic recommendations for surgery are identical to those during the (peri-)menopause as far as the management of symptomatic myomas are concerned.

HRT is not contra-indicated in the event of myoma, but the patient must be informed of the risk that they may worsen with treatment, and of the necessity of consulting a doctor if symptoms develop (grade C).

**QUESTION 3: ALTERNATIVES TO CONVENTIONAL SURGERY, TOTAL HYSTERECTOMY OR MYOMECTOMY**

**3.1 Role of embolization of the uterine arteries**

Firstly, due to lack of data, it is not possible to establish a recommendation on the general number and size of myomas that can be embolized. On the other hand, because of the risk of complications it is not advisable to treat a single submucosal intra-cavity myoma (type 0 or 1) or a single subserosal myoma with stalk (grade C) by embolization.

As far as the use of particles is concerned, non-spherical PVA particles are associated with a higher rate of occlusion of microcatheters than trisacryl microspheres. There is no difference between the various particles in terms of intensity of pain post-embolization, or analgesic dosage. There is no difference between non-spherical PVA particles and trisacryl microspheres (> 500 µm) in terms of clinical efficacy, reduction in uterine volume and rate of complications. PVA microspheres (Contour SE and Bead Block) are less clinically effective and have a lower myoma devascularization rate on MRI than trisacryl microspheres (Embosphere) (LP2). As a result, it is advisable to use particles larger than 500 µm (grade B) to embolize uterine myomas.

In terms of efficacy, embolization of the uterine arteries using non-spherical PVA particles or trisacryl microspheres larger than 500 µm effectively treats menorrhagia, compression symptoms and pelvic pain in the short-term in 90% of cases (LP1).

Efficacy in menorrhagia and compression symptoms is 75% at 5-7 years (LP1). The reduction in uterine volume at 6 months varies between 30 and 60%, and the reduction in volume of the dominant myoma varies between 50 and 80% at 6 months (LP1). The rate of complications during hospitalization is assessed as 3%. The level of complications in hysterectomy is less than 2% at 3 months. The definitive rate of amenorrhoea after embolization is less than 5% in women aged less than 45. Embolization has no effect on hormonal function in women aged less than 45 with a normal hormonal screen. The rate of secondary hysterectomy due to inefficacy or clinical recurrence is 13 to 28% at 5 years (LP1) according to studies.

Therefore, because it is an effective treatment and has low morbidity, it can be concluded that embolization of the uterine arteries is a credible therapeutic option for symptomatic myomas in women who do not wish to become pregnant (grade A).

There is no difference in efficacy on the symptoms of compression and on pelvic pain at 12 months and 24 months between embolization...
and hysterectomy by laparotomy; there is no difference in quality-of-life between embolization and hysterectomy by laparotomy at 12 months, 24 months or 5 years; there is no difference in level of satisfaction between embolization and hysterectomy by laparotomy at 24 months (LP1).

The rate of minor in-surgery complications is greater during embolization than during hysterectomy by laparotomy but the rate of major in-surgery complications is greater during hysterectomy by laparotomy than embolization. In the first 24 hours following treatment, pain evaluated on a visual analogue scale is more intense after hysterectomy by laparotomy than after embolization.

The rate of major complications at 6 weeks is greater after hysterectomy by laparotomy than after embolization. The rate of major complications at 1 year is no different after embolization than after hysterectomy by laparotomy (LP1). But re-interventions are more common after embolization than after hysterectomy in randomized trials: secondary hysterectomy is necessary after embolization in 13-24% of cases at two years, and up to 28% of cases at 5 years (LP1).

Duration of hospitalization, convalescence and time off work is shorter after embolization than after hysterectomy by laparotomy, and the cost of embolization is less than that of hysterectomy by laparotomy at 12 months, and at 24 months, even when the cost of scanning and re-interventions is taken into account (LP1).

Patients should be informed that embolization of the uterine arteries is an alternative to hysterectomy by laparotomy in the treatment of symptomatic myoma(s) if the patient has no wish to become pregnant (grade A). In the absence of any studies comparing embolization of the uterine arteries to hysterectomy by vaginal or coelioscopic route, no recommendation can be made. It is however desirable to inform the patient of this option in all cases where hysterectomy by vaginal or coelioscopic route is proposed.

At 6-26 months after treatment, there is no difference between embolization and myomectomy in terms of efficacy against symptoms of bleeding and compression (LP2). Neither is there any difference as far as reduction in uterine volume is concerned after embolization and myomectomy. There is no difference in quality-of-life 6 months after embolization and 6 months after myomectomy (LP3).

The rate of peri-operative complications at 30 days is no different (LP2), but the rate of complications at 6 months is greater after myomectomy (coelioscopy or laparotomy) than after embolization (LP2). However, the rate of re-interventions is greater after embolization than after myomectomy (LP2).

Duration of hospitalization, convalescence (LP2) and time off work (LP3) is shorter after embolization than after myomectomy (coelioscopy or laparotomy).

Finally, as regards fertility, FSH levels are commonly higher after embolization than after myomectomy. The rate of conception is higher after myomectomy than after embolization. The number of pregnancies that go to term is greater after myomectomy than after embolization. The rate of miscarriage is greater after embolization than after myomectomy (LP3).

There is no significant difference between embolization and myomectomy as far as the rate of premature labour, Caesarian, post-partum haemorrhage, pre-eclampsia or intrauterine growth retardation is concerned (LP2).

The patient must be informed that embolization of the uterine arteries is an alternative to myomectomy (by coelioscopy or laparotomy) in the treatment of symptomatic non submucosal myomas (type 0 or 1) in women who no longer wish to become pregnant (grade A).

Embolization of the uterine arteries is not the treatment of first choice in patients who wish to become pregnant (grade C). Patients must be informed of the risks if they wish to become pregnant following embolization (grade A).

Embolization of the uterine arteries prior to myomectomy (pre-operatively or combined technique) significantly reduces bleeding during surgery (LP3) and may be discussed on a case-by-case basis (grade C).

### 3.2 Role of destructive alternatives to surgical treatments other than embolization for myoma

#### 3.2.1 Myolysis or myoma destruction

The Nd:YAG laser has proven to be effective, but the cost of the equipment, the fragility of the fibres and the risk of post-operative adhesions have limited its development (LP4).

Myolysis with bipolar needles or microwaves are confidential techniques which do not have a role to date outside a research context.

Myolysis by radiofrequency is a technique that appears to be effective and relatively non-invasive but studies on larger cohorts are necessary (LP4). Myolysis by radiofrequency is an invasive alternative when carried out by coelioscopy, and less aggressive when conducted by vaginal route under ultrasound monitoring. However, only feasibility studies exist on a total of a few hundred patients; there are no comparative clinical trials.

Cryomyolysis is still an experimental procedure; the data currently available in the literature are not adequate to establish the efficacy and safety of the technique (LP4).
Focalized ultrasound treatment monitored by MRI or ultrasound presents a new opportunity; current results are encouraging after a learning curve; it is vital that patients are rigorously selected with treatment of single or double myomas, between 5 cm and 12 cm anterior and T2 weighted hypesignals on the MRI; approximately 10% of myomas are accessible by this technique if one wants to obtain a devascularization greater than 45%, which correlates to a success rate with symptoms in the order of 60-70% in the medium term (LP3). On the other hand, the reduction in volume of the myoma appears to be less (15-40%) than with other techniques (LP4). As far as myolysis is concerned, none of the current techniques can be recommended; the most advanced, best controlled and least aggressive technique appears to be ultrasound. Clinical research must be conducted on these techniques by comparative trials (comparing to surgery or embolization of the uterine arteries) in order to obtain levels of evidence that are sufficiently adequate to make recommendations. The patients benefiting from these techniques must be included in research protocols. To date there have been no publications that support or discourage myolysis in the event of a patient who wishes to become pregnant (grade C).

3.2.2 Coelioscopic ligation of the uterine arteries

Coelioscopic ligation of the uterine arteries is better tolerated but less effective than embolization (LP2) as it gives similar results at 6 months (30-50% reduction in volume and 50-80% reduction in symptoms) but less enduring results over time for identical indications; however, there is a restriction on accessibility in terms of uterine volume (LP2). Little has been written about the effectiveness of coelioscopic ligation of the uterine arteries in conjunction with myomectomy, however it significantly reduces bleeding (LP2).

Isolated coelioscopic ligation of the uterine arteries is a possible but less effective alternative in the long-term to embolization of the uterine arteries (grade B). To date there have been no publications that support or discourage coelioscopic ligation in the event of a patient who wishes to become pregnant (grade C). Due to lack of scientific evidence, acupuncture does not have a role among the wide variety of treatments for myoma.

3.3 Role of alternatives to hysteroscopic myomectomy in the treatment of myoma

In the case of submucosal myomas, techniques of endometrial reduction are effective (efficacy on the Higham score and haemoglobin level) alone or in combination with hysteroscopic resection of the myoma in women who have no wish to remain fertile (LP2).

Second-generation endometrial reduction techniques (thermocoagulation, hydrothermolation, destruction of the endometrium by radiofrequency or microwave) have shorter intervention times and fewer complications than first-generation techniques (hysteroscopic endometrial resection, Nd:YAG laser or rollerball ablation of the endometrium). These techniques are particularly interesting for patients at higher risk from anaesthetic or surgery (LP1). In addition, it appears that simultaneous destruction of the endometrium and submucosal myoma is more effective in controlling bleeding than myomectomy alone (LP4).

Not many pregnancies have been reported subsequently: of the order of 0.7% following hysteroscopic resection, and up to approximately 5% for second-generation techniques. Predominantly voluntary terminations of pregnancy, miscarriages and ectopic pregnancy have been described. These pregnancies also present specific risks to foetus and mother. More commonly than in the general population, early abortion/miscarriage is complicated by failure to evacuate due to cervical stenosis or synechiae (adhesions) and may result in hysterectomy (LP4).

In pregnancies that exceed 20 weeks of amenorrhoea, one finds significant rates of Caesarian, premature births, abnormalities of placental cord insertion and premature rupture of the membranes. More perinatal deaths and secondary hysterectomies have been found. In addition, two cases of uterine rupture have been described, one of which resulted in maternal death from a massive haemorrhage (LP4). Finally, the cost-efficacy of these types of management of myoma have yet to be evaluated.

It is therefore possible to use second-generation techniques of endometrial destruction to treat the meno-metrorrhagia associated with submucosal myomas in patients who have no further wish to become pregnant (grade B).

On the other hand, since pregnancies that occur in the course of these conservative treatments present a significant risk (LP4), the patient must be informed in advance of this fact (grade A). Effective contraception is advised (grade
C). It is also possible to perform hysteroscopic sterilization by Essure® during surgery while performing thermodestruction by Thermachoice® or bipolar resection (the only studies published to date) (LP4).

QUESTION 4: ROLE OF SUBTOTAL HYSTERECTOMY COMPARED TO HYSTERECTOMY FOR MYOMA

Preservation of the cervix during hysterectomy shortens the duration of surgery by approximately 17% [by laparotomy] (LP1). If coelioscopy is performed, preservation of the cervix does not shorten duration of surgery (LP2), probably due to uterine morcellation.

Preservation of the cervix decreases blood loss by laparotomy without affecting the rate of peri-operative transfusion (LP1), but with coelioscopy the blood loss is comparable between the two techniques (LP2).

Preservation of the cervix during hysterectomy reduces the occurrence of post-operative febrile episodes by laparotomy (LP1), whereas the rate of minor or major complications by coelioscopy is identical between the two techniques (LP2).

It does not affect the duration of post-operative convalescence by laparotomy (LP1); controversial study results from coelioscopy (LP4) do not allow any conclusions to be drawn.

Finally, as regards ureteral injury, there are no large-scale prospective randomized trials comparing total and subtotal hysterectomy. However, coelioscopy appears to increase the ureteral injury risk in hysterectomy overall (total and subtotal), and there appears to be no difference between total and subtotal, although the overall risk is very closely linked to the learning curve (LP2). On the other hand, coelioscopic subtotal hysterectomy seems to decrease the risk to the bladder compared to the incidence of bladder injury in total hysterectomy, but no randomized trials have been performed (LP3).

Because of the reduced (in laparotomy) or identical (in coelioscopy) complications, subtotal hysterectomy is an alternative to total hysterectomy for fibroids (grade B).

The risk of cancer of the cervical stump is approximately 0.05% after three normal cervical-vaginal smear tests (LP2). Patients who elect to preserve the cervix must be told that cervical screening will still be necessary (grade A). If there is a history of cervical dysplasia, there is a relative risk multiplied by three of developing cancer of the cervix (LP1). However, there are no cohort studies of women with a history of dysplasia who have been followed up after total and subtotal hysterectomy.

If a patient has a history of cervical dysplasia or is currently suffering from cervical dysplasia, a total hysterectomy should be performed rather than a subtotal hysterectomy (grade B).

Light menstrual bleeding which is not too annoying is reported in up to 20% of cases following subtotal hysterectomy. Conization of the endocervix during subtotal hysterectomy would reduce the incidence of menstrual bleeding from 10% to 1.4% (LP2). Inexperience of the surgeon increases the risk of surgical revision for this condition (LP4).

As far as the long-term functional aspects are concerned, preservation of the cervix by laparotomy or coelioscopy does not affect the quality of sexual intercourse following the intervention (LP1), or quality-of-life (LP1) (apart from improving body image); neither does it have any effect on urinary or digestive disorders or pelvic floor disorders (LP1).

There is no justification for performing a subtotal hysterectomy instead of a total hysterectomy in order to prevent pelvic function or sexual problems (grade A).

CONCLUSION

These guidelines on the therapeutic management of myomas supplement the 2000 and 2008 recommendations. They take stock of literature current in September 2011, which is sometimes very limited especially in terms of defining threshold number and size of myomas. The recommendations are intended for patients whose myomas have been properly diagnosed and for whom an accurate map has been drawn up using adequate scanning techniques (pelvic and endovaginal ultrasound in two or three planes with Doppler, contrast agent or hysterosonography if necessary; MRI as a second-line agent with T1, T2-weighted sections and gadolinium injection). These recommendations are accompanied by overall management of the patient, treating the myomas, their symptoms and consequences (anaemia, physical and psychological effect). Finally, they are intended as a basis for current good practice to be presented and discussed with the patient, while respecting their wishes and choices where feasible, and complying with medical ethics.

The bibliography of these guidelines is available at the end of each full article corresponding to a question that has been posed.