European Journal of Obstetrics and Gynecology 288 (2023) 90–107

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Review article

Management of women with abnormal uterine bleeding: Clinical practice guidelines of the French National College of Gynaecologists and Obstetricians (CNGOF)

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ARTICLE INFO

Keywords:
Guidelines
Abnormal uterine bleeding
Diagnosis
Treatment

ABSTRACT

Objective: To provide French guidelines for the management of women with abnormal uterine bleeding (AUB).
Design: A consensus committee of 26 experts was formed. A formal conflict-of-interest policy was developed at the beginning of the process and enforced throughout. The entire guidelines process was conducted independently of any industry funding (*i.e.* pharmaceutical or medical device companies). The authors were advised to follow the rules of the Grading of Recommendations Assessment, Development and Evaluation (GRADE®) system to guide assessment of quality of evidence. The potential drawbacks of making strong recommendations in the presence of low-quality evidence were emphasized.
Methods: The last guidelines from the *Collège National des Gynécologues et Obstétriciens Français* on the management of women with AUB were published in 2008. The literature seems now sufficient for an update. The committee studied questions within 7 fields (diagnosis; adolescents; idiopathic AUB; endometrial hyperplasia and polyps; type 0–2 fibroids; type 3 or higher fibroids; and adenomyosis). Each question was formulated in a PICO (Patients, Intervention, Comparison, Outcome) format and evidence profiles were compiled. The GRADE® methodology was applied to the literature review and the formulation of recommendations.
Results: The experts' synthesis work and the application of the GRADE method resulted in 36 recommendations. Among the formalized recommendations, 19 are strong and 17 weak. No response was found in the literature for

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https://doi.org/10.1016/j.ejogrb.2023.07.001
Received 9 March 2023; Received in revised form 25 June 2023; Accepted 1 July 2023
Available online 17 July 2023

14 questions. We chose to abstain from recommendations rather than providing advice based solely on expert clinical experience.
Conclusions: The 36 recommendations make it possible to specify the diagnostic and therapeutic strategies for various clinical situations practitioners encounter, from the simplest to the most complex.

Introduction

Abnormal uterine bleeding (AUB) is the leading cause of medical consultations for women aged 30 to 50 years. The last French guidelines issued by the *Collège National des Gynécologues et Obstétriciens Français* (CNGOF) on AUB management date back to 2008 [1]. In 2018, the United Kingdom NICE (*National Institute for Clinical Excellence*) issued new national guidelines for heavy menstrual bleeding in adults; ACOG (*American College of Obstetricians and Gynecologists*) also released guidelines on this topic in the USA, but focused on adolescents [2,3]. Since then, the availability of hormone therapy in France has tended to decrease, and the literature on therapies that are alternatives to hysterectomy has grown.

The objectives of these new guidelines are to define the clinical and other diagnostic strategies for AUB and to discuss treatment strategies according to the presumed aetiological diagnosis and the patient's age. These guidelines established according to the GRADE methodology are based on evidence obtained from the international literature [4,5]. They have been produced by experts using a multidisciplinary approach to provide an up-to-date and validated tool to help clinicians manage patients with AUB.

Materials and methods

The CNGOF named an organizing committee that in turn set up a group of experts, mainly gynaecologists but also radiologists belonging to other professional societies (e.g., the French Society of Radiology). The group included two patients, both representatives of patient organizations.

The organizing committee and expert coordinators initially determined the questions to be addressed and appointed experts responsible for each question. These were formulated using a PICO (Patients, Intervention, Comparison, Outcome) format. PubMed and Cochrane databases were used to perform an extensive search of the literature since 2000. The analysis only included publications in English or French issued through September 2020, or those considered essential by the experts.

We chose to address 37 questions divided into seven domains. These domains reflect the PALM-COEIN (polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified) classification developed by the International Federation of Gynaecology and Obstetrics (FIGO). It describes bleeding according to its functional or organic origin (AUB-X) and the FIGO classification of fibroids according to their situation in the uterus (types 0 to 7) [6–8]. The questions were chosen for three different reasons: their importance, the existence of significant advances since the previous guidelines, or the lack of consensus about them. The following domains and questions were used for the collection and analysis of the literature: Domain 1: Diagnosis of AUB (8 questions); Domain 2: AUB in adolescents (4 questions); Domain 3: Treatment of idiopathic AUB (AUB-N) (4 questions); Domain 4: Treatment of hyperplasia and endometrial polyps: AUB-P and AUB-M (3 questions); Domain 5: Treatment of type 0–2 fibroids (AUB-L) (5 questions); Domain 6: Treatment of type 2 or 3 (or higher) fibroids (AUB-L) (6 questions); Domain 7: Treatment of adenomyosis (AUB-A) (7 questions).

The evidence was presented and discussed and recommendations drafted in meetings, both in person and online. Proposed recommendations by the experts were then discussed until a consensus was reached. Each recommendation was labelled as strong or weak and a grade was assigned based on the strength of the supporting evidence (high, moderate, low, and very low). Strong recommendations (framed as "we recommend" or "clinicians should") should be applied to most patients, while weak recommendations (proposed as suggestions) require discussion and shared decision-making. Overall, 36 recommendations were drafted, 19 rated strong and 17 weak. The literature provided no conclusive response to 14 questions, and we preferred not to render a decision rather than to offer an expert clinical opinion based only on experience, rather than evidence.

The draft guidelines were sent to reviewers (listed below) from various specialties (gynaecologists, radiologists, paediatricians, endocrinologists, haematologists, and general practitioners). Their extensive comments resulted in modification or correction in the text of this draft.

These guidelines replace those from 2008, previously issued by the CNGOF on this topic. Nonetheless, in applying these guidelines, all doctors must exercise their own judgment, taking into account their own expertise and the specificities of their practice or establishment, to determine the method of diagnosis or treatment best suited to the specific patient.

Results

Background

AUB generally involves heavy menstrual bleeding, defined by frequent menstruation (more frequent than every 24 days), prolonged menstruation (longer than 8 days), and heavy flow volume (more than 80 mL of blood loss each period). The total volume of blood loss can be assessed by the pictorial blood assessment chart (PBAC) [9].

These guidelines do not cover lower genital haemorrhages (vulvar, vaginal, or exocervical) or vaginal bleeding associated with pregnancy, menopause, or other diseases (endocrinopathies and chronic diseases).

Detailed questioning enabling the establishment of a bleeding score based on family and individual history of heavy bleeding helps to identify women requiring an exploration of haemostasis. A gynaecological examination with a speculum is recommended to rule out lower genital bleeding [1].

The first laboratory test to prescribe for a woman consulting for AUB is a complete blood count to search for anaemia and thrombocytopoenia. A plasma hCG assay must be performed if pregnancy is suspected to be associated with upper genital tract bleeding. A hormonal work-up is unnecessary for AUB, except for TSH for women with signs or risk factors of hypothyroidism [1].

The first imaging examination to perform for women consulting for AUB is a pelvic ultrasound. Ideally, this examination should be performed by an expert consultant experienced in pelvic imaging of woman, with appropriate equipment used in optimal conditions. Magnetic resonance imaging (MRI) is habitually a second-line examination.

When an endometrial biopsy is necessary, the sample is usually taken with a Cornier pipelle.

Any current use of hormonal treatment that influences the menstrual cycle is likely to modify diagnostic and treatment strategies. Most of these treatments have an antigonadotropic effect: combined oral contraceptives (COC)), progestogens, GnRH analogues (GnRHa), danazol, anti-aromatases, selective progesterone receptor modulators (SPRMs) including ulipristal acetate (UPA), levonorgestrel-releasing intrauterine systems (52 mg) (LNG-IUS), etc.

The interventional radiology techniques studied for diagnosis and treatment of fibroids and adenomyosis are uterine artery embolization

(UAE) and high-intensity focused ultrasound (HIFU).

Conservative surgical treatment refers to the techniques of endometrial resection and endometrial ablation, and myomectomy for fibroids. The first-generation techniques are performed under hysteroscopy: endometrial resection by loop diathermy or ablation by *roller-ball*. The second-generation techniques allow thermocoagulation of the endometrium by thermal balloon endometrial ablation, with the intrauterine balloon heated to around 80 °C or a system emitting radiofrequency waves (radiofrequency ablation, RFA). Myomectomies can be performed by hysteroscopy (type 0–2 fibroids) or by laparoscopy and laparotomy (type 3 or higher).

Non-conservative — that is, radical — surgical treatment is a hysterectomy, preferentially by a laparoscopic or vaginal approach. Nonetheless, if technical or anatomical conditions do not allow a safe minimally-invasive approach, a laparotomy can be envisioned.

Domain 1: Diagnosis

PICO 1: For women with AUB, is a PBAC more effective than other techniques (chemical method or self-report) for assessing menstrual volume and reaching a specific AUB diagnosis?

R1.1 – In cases of diagnostic doubt for adults with AUB, we suggest a PBAC with a threshold of 100 (for the Higham score) to define the types of AUB.

Weak recommendation, Moderate quality of evidence.

R1.2 – In adolescents with AUB, we recommend a PBAC with a threshold of 100 (for the Higham score) to define types of AUB.

Strong recommendation, Moderate quality of evidence.

Rationale

The performance of the PBAC for assessing AUB, as validated by the alkaline haematin technique, is satisfactory with its sensitivity ranging from 58% to 97% and its specificity from 8% to 96% [10]. No data compare the PBAC and self-report for adult women complaining of AUB. There is no evidence supporting the systematic performance of PBAC in all women to establish a diagnosis of AUB, except when diagnostic doubt exists. One study has compared the PBAC and self-report in adolescents: more than 60% of adolescents who considered their periods normal had a PBAC > 100 [11]. These results thus favour PBAC use in this age group.

PICO 2: For women with AUB, is a haematological work-up including a complete blood count and ferritinaemia more effective than a complete blood count alone for assessing the extent and consequences of this bleeding?

No Recommendation

Rationale

The prevalence of iron deficiency among women is estimated at 10% and that of anaemia at 2% to 5% [12]. The prevalence of symptoms associated with isolated iron deficiency is not known, but they are generally minor, non-specific, and not severe. We cannot issue a recommendation about the utility of prescribing a ferritinaemia measurement together with a complete blood count in women reporting AUB given the absence of any study comparing this combination with the complete blood count alone.

PICO 3: In women with AUB not using hormonal treatment (contraceptive or other), are imaging examinations more effective than laboratory haemostasis testing as a first-line method for establishing an aetiological diagnosis?

R1.3 – The following tests are recommended for adults with AUB not using any hormonal treatment and with normal ultrasound findings: a complete blood count, a coagulation work-up (prothrombin time, activated clotting time, and fibrinogen), and testing for von Willebrand disease (von Willebrand factor [vWF], Factor VIII, vWF activity, and vWF antigen).

Strong recommendation, Low quality of evidence.

Rationale

There are no available data comparing the performance of imaging and laboratory testing. Only one third of adults with AUB have ultrasound abnormalities (PALM) [13,14]. In other women without an aetiology found on pelvic ultrasound, a complete blood count, a coagulation work-up, and a search for von Willebrand disease must be performed.

PICO 4: In women with AUB not using hormone treatment (contraceptive or other), without haemostasis disorders, and with normal pelvic ultrasound findings, is a pelvic MRI necessary to establish an aetiological diagnosis?

R1.4 – In a woman with AUB not using hormone treatment and without any haemostasis disorders, we suggest that a pelvic MRI not be performed unless the pelvic ultrasound performed by an expert shows abnormalities.

Weak recommendation, Very low quality of evidence.

Rationale

No recent study has evaluated the utility of MRI among women with AUB and normal pelvic ultrasound findings. The negative predictive value (NPV) was 82% for two-dimensional (2D) pelvic ultrasound in the two old studies that considered the question [15,16]. The estimated NPV of 3D ultrasound is 92% (16). MRI has an NPV of 86% for the diagnosis of uterine cavity abnormalities (17). The data in the literature show that a pelvic ultrasound, when performed by a specialist ultrasonographer and with normal findings, enables uterine pathology to be ruled out [15,16].

PICO 5: In women with AUB not using hormonal treatment (contraceptive or other), without haemostasis disorders, and with abnormal pelvic ultrasound findings, is a pelvic MRI necessary to support an aetiological diagnosis?

R1.5 – In women with AUB not using hormonal treatment whose pelvic ultrasound reveals one or more type 2 (or higher) uterine fibroids, a pelvic MRI is recommended to map these fibroids before myomectomy (if the ultrasound is considered insufficient) or interventional radiology.

Strong recommendation, Low quality of evidence.

R1.6 – We suggest that an additional pelvic MRI not be performed in women with AUB not using hormonal treatment whose pelvic ultrasound findings show polyps or adenomyosis, unless there is doubt about the diagnosis of adenomyosis.

Weak recommendation, Low quality of evidence.

Rationale

Three principal uterine disorders are considered when the ultrasound findings are abnormal: polyps, fibroids, and adenomyosis. For the diagnosis of polyps, MRI is no more valuable than 2D ultrasound [18]. Hysterosonography performs better than MRI [17,19]. For the diagnosis of fibroids, MRI performs no better than ultrasound when the fibroid has a typical appearance. MRI is better than ultrasound for specifying fibroid size, site, and morphology and therefore for determining the treatment strategy. For submucosal fibroids, hysterosonography performs better

than both MRI and ultrasound [17,18,20]. For adenomyosis, meta-analyses estimating the pooled diagnostic properties of MRI and of ultrasound have reported no significant difference between them, with the reference diagnosis based on the pathology examination of the hysterectomy specimen [21]. A recent study with MRI results as the reference suggests that ultrasound sensitivity for a diagnosis of adenomyosis is low [22].

PICO 6: In women with AUB not using hormonal treatment (contraceptives or other) with normal laboratory results and a pelvic ultrasound suggestive of an intracavitary pathology, does hysteroscopy perform better than the other imaging examinations (hysterosonography, pelvic MRI) for establishing an aetiological diagnosis?

R1.7 – We suggest that complementary examinations (diagnostic hysteroscopy, hysterosonography or pelvic MRI) not be routinely ordered for women with AUB who are not using hormonal treatment, who have normal laboratory results, and whose pelvic ultrasound enabled diagnosis of an intracavitary pathology.

Weak recommendation, Low quality of evidence

R1.8 – In cases of doubt about the ultrasound diagnosis of an intracavitary pathology, we recommend that a hysteroscopy or a hysterosonography be performed to establish a diagnosis of one or more polyps or type 0–2 fibroids, or an MRI if the development of a submucosal fibroid (types 1 and 2) is suspected and the preceding examinations cannot be carried out.

Strong recommendation, Low quality of evidence

Rationale

Ultrasound, hysteroscopy, and hysterosonography all have good – and similar – diagnostic performance for affirming the diagnosis of an intracavitary pathology [17,19,23].

MRI performs less well than hysterosonography for the diagnosis of polyps, but better than hysteroscopy for the diagnosis of a submucosal fibroid [17,19]. No evidence supports preferring to recommend one or the other of these methods to characterize intracavitary uterine abnormalities. The choice can be based on the feasibility and acceptability of hysterosonography at the same time as ultrasound (in cases of diagnostic doubt), of outpatient hysteroscopy if the facility allows it, and the possibility of an MRI (in cases of diagnostic doubt), taking into account the availability of the device and the cost of the procedure.

PICO 7: In an adult woman with AUB and a thickened endometrium on pelvic ultrasound, is an endometrial biopsy necessary to enable a diagnosis of endometrial hyperplasia?

R1.9 – In adults with AUB, we recommend an endometrial biopsy if the endometrial thickness exceeds 15 mm.

Strong recommendation, Low quality of evidence

R1.10 – In adults with AUB, we recommend an endometrial biopsy in the presence of risk factors for endometrial cancer (perimenopause, high body mass index, diabetes, nulliparity, genetics).

Strong recommendation, Low quality of evidence

Rationale

AUB is associated with a risk of complex or atypical hyperplasia or cancer in 1.7% to 4.9% of cases [24–26]. A thickened endometrium on pelvic ultrasound is associated with a risk of endometrial hyperplasia in 7.6% of cases [26]. Nonetheless the ultrasound threshold for abnormal endometrial thickening among women during a period of normal menstruation has not been clearly established: 12 to 15 mm depending on the series [27,28]. Moreover the maximum values of endometrial thickness observed during the secretory phase of a normal menstrual cycle (12 to 14 mm) must also be taken into account.

Studies have evaluated the diagnosis of abnormal histology, defined by complex and/or atypical hyperplasia or carcinoma in cases of menometrorrhagia, regardless of endometrial thickness. In premenopausal women with AUB, abnormal endometrial histology is significantly correlated with age, body mass index, diabetes, nulliparity, and endometrial thickness greater than 12 mm [26]. An endometrial biopsy must therefore be performed among women with risk factors for endometrial cancer.

PICO 8: In women with AUB and using hormonal contraception, are modifications of the treatment regimen preferable to diagnostic exploration (imaging or biopsy) as a first-line treatment?

No Recommendation

Rationale

Unexpected vaginal bleeding and/or spotting in users of hormonal contraception are frequent events: COC (30% to 50%), oral progestogens (30%), and contraceptive implant (34%) [29–32]. Nonetheless, the cases of AUB defined by a PBAC bleeding score >100 occurring during the use of hormonal contraception are rarer events that are difficult to quantify.

There are no data in the literature that define a diagnostic strategy or treatment orientation for women with AUB who are using hormonal contraception. Professional societies have formulated expert opinions suggesting the performance of a work-up to search for a cause that could explain the onset of the bleeding according to the clinical context before proposing to modify the treatment regimen [33,34]. The differential diagnoses to rule out are pregnancy, infection, drug interaction, or an organic uterine pathology. Numerous treatment options have been tested for short-term control of unexpected bleeding in users of contraception, especially of pure progestogens. These options include combined oestrogens, tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs), and mifepristone. The results have been disparate and the low power of the studies means that no management can yet be proposed [35].

In adults with AUB using hormonal contraception, there is no evidence for preferring either a diagnostic exploration (imaging or biopsy) or modifications of the treatment regimen.

Domain 2: Adolescents

PICO 9: In adolescents with AUB, is haemostasis testing a more effective first-line examination than imaging for establishing an aetiological diagnosis?

R2.1 – In adolescents with AUB, we recommend haemostasis testing as a first-line work-up.

Strong recommendation, Low quality of evidence

Rationale

The prevalence of haemostasis disorders in adolescents with AUB is on the order of 10% to 65% according to series that come mainly from specialised centres [36–44]. Their diagnosis involves complementary testing (especially haematological, for example, for von Willebrand disease) that will be necessary throughout their lives. The other causes of AUB that can be diagnosed by pelvic ultrasound are relatively rare in adolescents (1.3%) [45].

There are no existing studies comparing the diagnostic performance of a haemostasis work-up with that of a pelvic ultrasound in adolescents with AUB. Nonetheless, in view of the high prevalence of haemostasis disorders and the low prevalence of ultrasound abnormalities in this population, haemostasis testing is indicated first.

PICO 10: In adolescents with AUB and normal haemostasis results, is pelvic MRI more effective than pelvic ultrasound for establishing an aetiological diagnosis?

R2.2 – In adolescents with AUB and normal haemostasis results, we suggest performing a pelvic ultrasound rather than an MRI as the first-line imaging work-up.

Weak recommendation, Low quality of evidence

Rationale

Organic aetiologies of AUB are rare in adolescents (1.3%) [45]. A pelvic ultrasound can be performed by the suprapubic or transvaginal route, by expert ultrasonographers, and this equipment is often simpler to access than MRI. Nonetheless, the performance of the suprapubic route can be limited by parietal echogenicity, and the transvaginal route may not be possible for teens with no previous sexual activity.

No study has compared the diagnostic performance of MRI and pelvic ultrasound in adolescents with AUB and normal haemostasis findings. Pelvic MRI has not been evaluated in adolescents with AUB. Pelvic MRI does not appear to perform better than pelvic ultrasound for a pelvic evaluation of adolescents with AUB [46].

PICO 11: In adolescents with AUB, normal haemostasis findings, and normal pelvic imaging, is hormonal treatment (contraceptive or other) more effective and better tolerated than non-hormonal therapies for treating AUB?

No Recommendation

Rationale

Although it is frequent and disabling, few studies have examined treatment options for idiopathic AUB in adolescents. Moreover, the various treatment trials for adults include no adolescent "subgroup".

The objective of hormonal therapy is to obtain long-term oligomenorrhoea or amenorrhoea, while anti-inflammatory or anti-fibrinolytic treatments are administered on an ad hoc basis. One randomized trial comparing tenoxicam to a COC provided evidence supporting the use of this NSAID at the acute phase of idiopathic AUB: shorter hospitalizations (6.9 +/− 2.9 d vs 8.5+/−2.6 d, $P = 0.001$); significant improvement in haemoglobin concentration (11.5 +/−1.8 g/dL vs 10.4 +/− 1.5 g/dL, $P = 0.05$) [47].

Other studies, comparative or not, have shown that the effectiveness of tranexamic acid in reducing the menstrual flow is similar to that of COC (44). The effectiveness and tolerability of hormonal treatments vary according to their routes of administration (intrauterine versus oral) but also between patients. One study showed an improvement of symptoms in 93% of adolescents treated by the placement of an LNG-IUS [48]. Finally, for women wanting contraception, among 193 women aged 18 to 25 years, continuation of treatment to the end of one year was similar for EPC (73%) and LNG-IUS (80%), $P = 0.28$ [49].

In adolescents with idiopathic AUB, all treatments are effective and well tolerated. The quality of evidence of the only randomized study was low. In the absence of other comparative studies among adolescents, it is not possible to recommend one treatment over any other.

PICO 12: In adolescents with AUB, abnormal haemostasis findings, and normal pelvic imaging, is hormonal treatment (contraceptive or other) more effective and better tolerated than non-hormonal therapies for treating AUB?

No Recommendation

Rationale

The treatment of adolescent AUB secondary to a haemostatic abnormality is dominated by the specific management for the specific haemostatic disorder [50].

The objective of hormonal therapy is to obtain long-term oligomenorrhoea or amenorrhoea, while anti-fibrinolytic treatments are administered on an ad hoc basis.

No study has compared the effectiveness and tolerability of treatments, hormonal or not, in adolescents with AUB and a haemostasis disorder.

In the absence of a study focused on a population of adolescents with abnormal haemostasis findings and normal imaging, it is not possible to recommend one treatment rather than another. We recommend that French adolescents with AUB and abnormal haemostasis findings be referred to a reference hospital for rare gynaecological diseases with expertise in bleeding disorders (French coordinating centre: Necker Hospital, Paris. https://www.maladiesrares-necker.aphp.fr/pgr/).

Domain 3: Idiopathic AUB (adults) (Fig. 1)

PICO 13: In women with idiopathic AUB, are hormonal therapies more effective and better tolerated than non-hormonal therapies for treating AUB?

R3.1 – In women with idiopathic AUB and wanting to become pregnant soon, we suggest a non-hormonal first-line treatment, with a preference for anti-fibrinolytic agents.

Weak recommendation, Low quality of evidence.

R3.2 – In women with idiopathic AUB and no desire for pregnancy in the short-term, we recommend as a first-line treatment an LNG-IUS (52 mg) (in the absence of any contraindication).

Strong recommendation, Moderate quality of evidence

Rationale

Several studies grouped for meta-analyses make it possible to compare the effectiveness and tolerability of different types of treatment:

1) Oral hormonal treatment vs non-hormonal treatment. Norethisterone acetate treatment administered in the second half of the menstrual cycle is inferior to treatment by anti-fibrinolytic agents (tranexamic acid) for control of AUB, patient satisfaction (OR 0.31; 95% CI 0.13, 0.71) and QoL [51]. Medroxyprogesterone acetate (MPA) used 20 days a month is inferior to tranexamic acid for duration of bleeding and QoL (failure rate 28.9% vs 6.1%, $P = 0.003$) [52].
2) Comparison between medical non-hormonal treatments. Tranexamic acid (anti-fibrinolytic) was more effective than mefenamic acid (NSAID) and etamsylate (anti-fibrinolytic) for the control of AUB, defined by the objective and subjective improvement of symptoms (RR 1.4; 95% CI 1.2, 1.7) [53].
3) The LNG-IUS vs other oral hormonal and non-hormonal therapies. The LNG-IUS is superior to non-hormonal treatment (tranexamic acid) and oral hormonal treatment (norethisterone acetate, COC) for AUB control, QoL, and satisfaction (RR 1.3; 95% CI 1.0, 1.6) [54].

Side effects to non-hormonal oral treatments are very rare. Tranexamic acid is contraindicated in women with a history of venous and arterial thromboembolic events and in the case of additional thromboembolic risk factors. In a case-control study assessing the risk of venous thromboembolism associated with AUB treatment (134 cases and 552 controls), the adjusted OR associated with the use of tranexamic acid was 3.2 (95% CI 0.7, 15.7) versus 5.5 (95% CI 2.1, 14.4) for mefenamic acid, and 2.4 (95% CI 1.0, 5.8) for norethisterone acetate [55].

For hormonal therapy, progestogens (specific compounds not specified) were associated with venous accidents in a WHO case-control

study (7 cases vs 12 controls), adjusted OR 5.9 (95% CI 1.2, 30.1) [56]. Oral use of MPA has not been studied alone, but the risk of thromboembolism rises when MPA is administered by injection for contraception (OR 3.0) [57]. Nonetheless, the relative risk of venous thromboembolisms associated with treatment by chlormadinone acetate (a macroprogestogen used for AUB in France) is not significant: RR 0.8; 95% CI 0.2, 3.9 [58]. Comparison of oral progestogen treatment and the LNG-IUS with non-hormonal treatments found no difference in the onset of side effects. On the other hand, use of the LNG-IUS is associated with fewer treatment failures and better treatment continuation.

PICO 14: In women with idiopathic AUB who no longer desire future fertility, are medical treatments more effective and better tolerated than surgical treatment for AUB?

R3.3 – For women younger than 42 years with idiopathic AUB who no longer desire future fertility, we recommend offering the LNG-IUS (52 mg) (in the absence of contraindications) as a first-line treatment because of its effectiveness and its contraceptive benefits.

Strong recommendation, Moderate quality of evidence

R3.4 – For a woman 42 years or older with idiopathic AUB wishing to keep her uterus but not her fertility, we suggest that endometrial ablation, because of its lower rate of side effects, be offered as a first-line treatment rather than the LNG-IUS (52 mg).

Weak recommendation, Moderate quality of evidence.

Rationale

Several studies grouped for different meta-analyses allow a comparison of the effectiveness of different types of treatment:

1) Medical treatment (excluding the LNG-IUS) vs conservative (endometrial ablation) or radical (hysterectomy) surgical treatment. Medical treatment is inferior to conservative and radical surgical treatment for control of AUB and for the patient's QoL, tolerance, and satisfaction at 1 to 2 years later [59–63]. Longer-term data (2–5 years) do not find differences for bleeding control or satisfaction, but this result must be considered in light of both the poverty of the available literature and the high proportion of patients treated medically who subsequently have surgical treatment [62,63]. Medical treatment is associated with more adverse effects than conservative surgical treatment [59–61]. It is also associated with more frequent recourse to repeat surgery than either conservative or radical surgical treatment [59–63].
2) LNG-IUS vs conservative surgical treatment (endometrial ablation). These did not differ for amenorrhoea rate or patient satisfaction at 1 year [54]. QoL at 1 year and satisfaction at 2 years (RR 1.1; 95% CI 1.0, 1.3) favoured surgery, but at 5 years both were better for the LNG-IUS: RR 1.5; 95% CI 1.1, 1.9. The LNG-IUS was associated with more side effects than endometrial ablation: RR 2.1; 95% CI 1.4, 2.9. The risk of a secondary hysterectomy was higher after insertion of an LNG-IUS than after endometrial ablation at one year (RR 2.6; 95% CI 1.5, 4.4), but this risk disappears after a year (RR 1.1; 95% CI 0.5, 2.6) [54]. The risk of hysterectomy is higher after conservative surgery than after LNG-IUS placement among women up to the age of 42 years (RR 5.3; 95% CI 1.2, 22.9), but this risk disappears after the age of 42 (RR 0.5; 95% CI 0.2, 1.2) [64].
3) LNG-IUS vs radical surgical treatment (hysterectomy). The improvement of the PBAC at 2 years is clearly superior for radical surgery [54]. There is no difference in terms of either patient satisfaction at 5 years (RR 1.0; 95% CI 0.9, 1.1) or QoL. Radical surgery is associated with an excess risk of early deep infection (RR 5.9; 95% CI 1.5, 20), while the LNG-IUS had more long-term adverse effects, especially ovarian cysts (RR 2.7; 95% CI 1.2, 6.0) and dorsolumbar pain (RR 1.7; 95% CI 1.2, 2.4). The risk of recourse to secondary surgery is logically increased with an LNG-IUS.
4) Comparison between conservative surgical treatments. There is no difference in effectiveness in terms of improvement in PBAC, amenorrhoea rate, or patient satisfaction between the first-generation conservative surgical treatments and the subsequent generations [65]. A large retrospective cohort study shows that the failure rates of the first- and second-generation techniques are respectively 13% and 10% at 18 months ($P < 0.001$) and 22% and 19% at 60 months (NS) [66]. The second-generation techniques are associated with shorter operative time and are performed under local anaesthesia more often [65]. On the other hand, they are subject to technical failure more often. The risk of major complications is higher with the first-generation treatments in the meta-analysis, but that was not observed in the retrospective French cohort [65,66]. The risk of repeat surgery in the 5 years after initial management did not differ between the groups.

PICO 15: In women with idiopathic AUB eligible for surgery and not desiring future fertility, is conservative surgical treatment as effective and well tolerated as hysterectomy?

R3.5 – In a woman with idiopathic AUB eligible for surgical treatment and desiring to keep her uterus, but not future fertility, we recommend that a technique of endometrial resection or ablation be proposed as a first-line treatment.

Strong recommendation, Moderate quality of evidence

R3.6 – In a woman with idiopathic AUB eligible for surgical treatment and without any desire to preserve her uterus, we recommend that hysterectomy by a laparoscopic or vaginal route be proposed as a first-line treatment.

Strong recommendation, Low quality of evidence.

Rationale

Conservative surgical treatment (endometrial resection or ablation) and hysterectomy are both effective and well-tolerated techniques for treating idiopathic AUB in adults with no desire for a future pregnancy. The improvement in bleeding (PBAC scores) was better among women treated by hysterectomy [67]. The two groups had similar and high rates of satisfaction at 1 year (77% vs 82%; RR 0.9; 95% CI 0.8, 1.0) and 4 years after surgery (68% vs 76%: RR 0.9; 95% CI 0.8, 1.0), but the QoL evaluation tended to be better after hysterectomy for some criteria [68–72].

The risk of repeat surgery when the initial treatment failed within 4 years was higher among women treated conservatively (38% vs 1%; RR 36.3; 95% CI 5.1, 259.2) [67]. The risk of postoperative complications (infection, pelvic or parietal haematoma, or transfusion) was higher among women treated by hysterectomy (6–48%) than by endometrial ablation (4–12%). Conservative surgical treatments were associated with shorter times than hysterectomies for all relevant intervals: operative time, length of hospital stay, convalescence, and time to return to work. The initial studies compared the first-generation techniques of endometrial resection/ablation to transabdominal hysterectomy, while more recent studies have compared the second-generation techniques of endometrial ablation to total or subtotal hysterectomy by the laparoscopic or vaginal route. The differences in terms of the length of the intervention, hospitalization, convalescence, and time to return to work persist in recent studies, but are less pronounced than in the initial studies [69,70,72–74].

The data from the literature do not support a recommendation in favour of conservative or radical surgery for all women, because both techniques have a good benefit (efficacy)/risk (complications) balance. Nonetheless, an endometrial resection or ablation can be proposed in first line to women who desire to keep their uterus, to diminish their

postoperative morbidity and the duration of their convalescence. A hysterectomy can be proposed as a first-line treatment for women who do not want to keep their uterus, to reduce the risk of repeat surgery for recurrent AUB by using a laparoscopic or vaginal approach performed by experienced surgeons in well-equipped operating rooms [75].

PICO 16: In women with AUB due to a benign uterine pathology, is the correction of preoperative anaemia associated with a decrease in surgical morbidity and mortality?

R3.7 – In women with AUB due to a benign uterine pathology, we suggest that preoperative anaemia be corrected by iron supplementation — associated or not with hormonal therapy (GnRHa) — to reduce surgical morbidity and mortality.

Weak recommendation, Low quality of evidence.

Rationale

Preoperative anaemia is associated with an increase in mortality, morbidity, and perioperative transfusion rates in most surgical specialties [76,77]. Three retrospective studies from large databases confirm this information for the population of non-menopausal women who are candidates for gynaecological surgery (hysterectomy, myomectomy) for benign uterine pathologies: mortality (0.5% vs 0.1%; adjusted OR 2.4; 95% CI 1.1, 5.4, $P < 0.001$), and morbidity 5.1% vs 2.5%; adjusted OR 1.8; 95% CI 1.5, 2.2, $P < 0.001$) [78–80].

The modes for the correction of anaemia available before surgery in non-menopausal women are GnRHa, iron supplementation of iron-deficiency anaemia, progestogen treatments, and finally haemostatic substances. The GnRHa used before surgery for fibroids allows the gain of around one point of haemoglobin [81]. One study has identified perioperative transfusion as a factor related to increased postoperative morbidity for laparoscopic hysterectomy for benign diseases [82]. Intermittent oral iron supplementation in non-menopausal women can reduce anaemia [83]. No studies in gynaecology assess preoperative intravenous (IV) iron supplementation aimed at diminishing recourse to perioperative transfusion. A Cochrane review published in 2019 on this subject in other surgical domains was not able to reach a conclusion [84]. More recently, a randomized controlled trial evaluated preoperative intravenous iron supplementation for anaemia before abdominal surgery (including 30% with gynaecological indications): this supplementation allowed partial correction of the anaemia, but had no impact on the rates of transfusion, mortality, or complications at one month, nor on QoL [85].

The widely recognized principle of "patient blood management" in surgery is defined as the detection of preoperative anaemias (iron-deficient or not) and their correction by means other than transfusion whenever possible [86]. Thus, GnRHa and iron supplementation used before surgery are well tolerated, except for menopausal symptoms for the GnRHa and gastrointestinal disorders for oral iron.

Overall, no study has evaluated the effect of correcting preoperative anaemia on the morbidity and mortality of gynaecological surgery indicated for AUB. Nonetheless, the literature confirms that preoperative anaemia is a risk factor for postoperative morbidity and mortality in non-menopausal women undergoing an abdominal hysterectomy or myomectomy. The indirect proof from other specialties and the strong impact of preoperative anaemia on morbidity provide incentives to correct preoperative anaemia.

Domain 4: Endometrial hyperplasia and polyps

PICO 17: In women with AUB associated with non-atypical endometrial hyperplasia, are medical treatments more effective and better tolerated than conservative surgical treatment for treating AUB? (Fig. 1)

R4.1 – In women with AUB associated with non-atypical endometrial hyperplasia and desiring to remain fertile, we recommend proposing treatment by the LNG-IUS (52 mg) as a first-line treatment (in the absence of contraindications).

Strong recommendation, Moderate quality of evidence.

R4.2 – We suggest that women with AUB associated with non-atypical endometrial hyperplasia and without any desire to remain fertile be offered either treatment by the LNG-IUS (52 mg) (in the absence of contraindications) or endometrial resection or ablation.

Weak recommendation, Low quality of evidence.

Rationale

The AUB associated with non-atypical endometrial hyperplasia is associated with a low risk of neoplastic degeneration (1% to 3%) [87]. The literature has evaluated in particular the various medical treatments for women with non-atypical endometrial hyperplasia who desire future fertility.

In terms of effectiveness for the regression of hyperplasia, the LNG-IUS is superior to oral progestogens at 6 months (89% vs 72%; OR 2.9; 95% CI 2.1, 4.1), at 12 months (80% vs 51%; OR 3.8; 95% CI 1.7, 8.2), and at 24 months (90% vs. 56%, OR 7.5; 95% CI 2.5, 21.8) [88,89]. For endometrial hyperplasia, the LNG-IUS is associated with fewer secondary hysterectomies (OR 0.26; 95% CI 0.15, 0.46), fewer treatment withdrawals due to adverse effects (OR 0.41; 95% CI 0.12, 1.35) and more women reporting satisfaction (OR 5.3; 95% CI 2.5, 11.1)), compared with non-intrauterine progestogens [89].

Other progestogens, such as intramuscular MPA, and an aromatase inhibitor (letrozole), are effective treatment options with a regression rate for lesions exceeding 90% at 6 months [90,91]. Nonetheless, these substances are either not available in France or do not have a marketing authorization, so that medical treatment is limited to the LNG-IUS alone. No studies have evaluated GnRHa in endometrial hyperplasia without atypia.

Among women who do not desire to remain fertile, conservative surgical treatment by endometrial ablation — either initially or if medical treatment fails — enables normalization of the AUB symptoms (97% reduction) and improvement of QoL (80%) with a low risk of major intraoperative complications (3%) [92].

Overall, for progestogens, intrauterine administration must be proposed preferentially, in view of its superiority for effectiveness, tolerability, and availability. Despite the absence of comparative studies between medical treatment and conservative surgery among women with non-atypical endometrial hyperplasia, no apparent difference in effectiveness appears to exist between these two strategies. A first- or second- generation conservative surgical treatment can be proposed initially or after the failure of medical treatment to women who do not desire to remain fertile. There is no evidence for systematic endometrial biopsy or ultrasound follow-up in women with AUB associated with non-atypical endometrial hyperplasia, providing the outcome is successful.

PICO 18: In women with AUB associated with atypical endometrial hyperplasia wishing to remain fertile, are medical treatments an effective and safe alternative to hysterectomy? (Fig. 2)

No Recommendation

Rationale

Patients with AUB associated with atypical hyperplasia have a risk of progression to cancer that ranges from 8% to 29% [87].

Among women with AUB associated with atypical hyperplasia, wishing to remain fertile, hormonal treatment (progestogens alone or associated with GnRHa) allow a regression rate of 66% to 85%, a

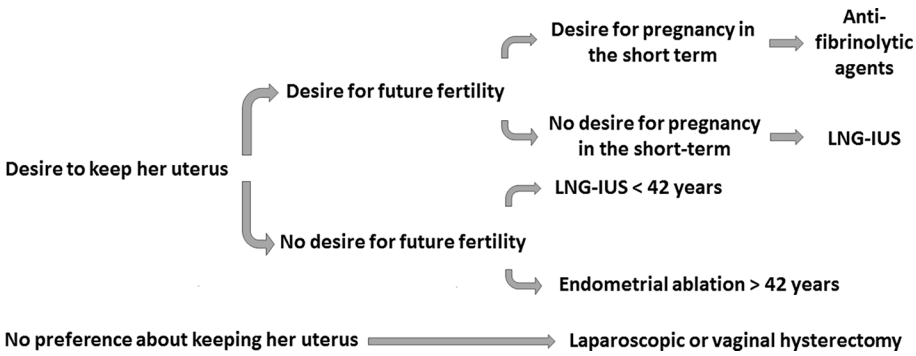

Fig. 1. Decision tree for treatment of women with idiopathic AUB or non-atypical endometrial hyperplasia. Notes: AUB: abnormal uterine bleeding; LNG-IUS: levonorgestrel intra-uterine system 52 mg.

recurrence rate of 23% to 30%, and a live birth rate of 26% to 41% with a follow-up on the order of 3 years [93–96].

Megestrol acetate, at a dose ranging from 40 to 100 mg, enables a histologic regression rate of endometrial hyperplasia with atypia of 66% to 100% [97,98]. Nonetheless, the risk of recurrence is approximately 30% [96].

The effectiveness of the LNG-IUS is similar to that of the principal oral progestogen treatments (norethisterone and MPA) with a histological regression rate of atypical hyperplasia ranging from 76% to 100% [95,99]. The adverse effects of the LNG-IUS are similar to those of oral progestogen, except for spotting, which is 2–3 times more frequent with this device [99].

Associated with other progestogen treatments or conservative surgery (endometrial ablation), GnRHa may have benefits [100–102]. The adverse effects secondary to menopause that it may induce have not been evaluated in this situation, especially the risk of osteoporosis.

Overall, in women with AUB associated with atypical endometrial hyperplasia wishing to remain fertile, medical treatments can be an alternative to hysterectomy, but there is nonetheless a risk of progression or recurrence during or after treatment. This rare situation requires cooperative multidisciplinary management, proposed especially by the PREFERE network in France, headquartered at Bichat Hospital, Paris https://hopitauxnord-u-pariscite.aphp.fr//centre-prefere/prefere-centre-de-reference/.

PICO 19: In women with AUB associated with a benign endometrial polyp and not considering a future pregnancy, is first- or second-generation conservative surgical treatment associated with polyp resection more effective and better tolerated than resection of the polyp alone to treat the AUB and prevent its recurrence? (Fig. 3)

R4.3 – In women with AUB associated with a benign endometrial polyp and not considering a future pregnancy, we suggest that polyp resection be combined with a first-generation (or by extension, second-generation) conservative surgical treatment.

Weak recommendation, Very low quality of evidence.

Rationale

AUB due to a benign uterine polyp is a standard situation, but the literature about its frequency and causal link is sparse. When a polyp is identified in woman with AUB, hysteroscopic exploration is indicated to identify its histologic type and to excise it [103].

Three retrospective studies have compared the resection of a polyp associated with endometrial resection or ablation to resection of the polyp alone:

1) In a series of 367 women with a median follow-up of 40 months, symptom regression (98% vs 93%, $P < 0.05$) and satisfaction (97% vs 91%) were best with resection of both polyp(s) and endometrium [104];
2) In a series of 78 women, there was no difference in effectiveness, judged by the criterion of no repeat surgery at 4 years (54% vs 41%; $P = 0.08$) [105];
3) The reintervention rate was higher in the case of polyp resection alone (15% vs 0%) in a series of 34 women [106].

These data tend to favour the combination of 2 treatments during the same operative hysteroscopic intervention. The risk of complications (uterine perforation, fluid absorption) is theoretically higher when the polyp resection is combined with endometrial ablation than when the resection takes place alone. Nonetheless this risk is very rare for both techniques and therefore acceptable.

Domain 5: Type 0–2 fibroids (Fig. 4)

PICO 20: In women with AUB associated with one or more type 0–2 fibroids and with no immediate desire for pregnancy, are hormonal treatments more effective and better tolerated than hysteroscopic myomectomy for treating AUB?

No Recommendation

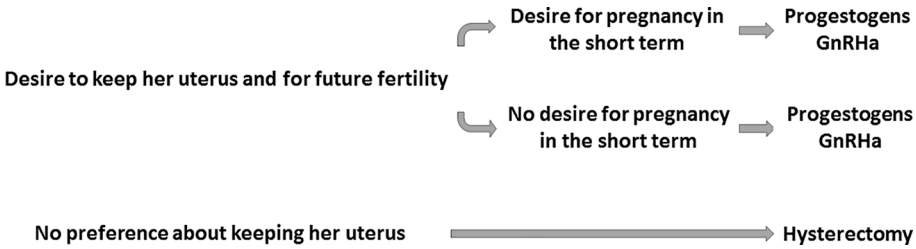

Fig. 2. Decision tree for treatment of women with AUB and atypical endometrial hyperplasia. Notes: AUB: abnormal uterine bleeding; GnRHa: GnRH analogues.

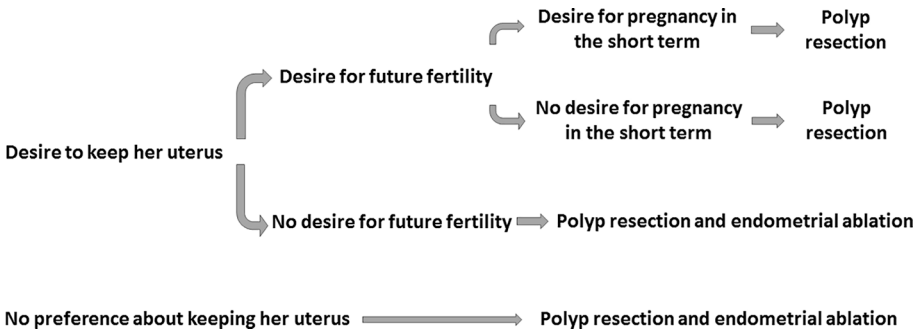

Fig. 3. Decision tree for treatment of women with AUB and endometrial polyp. Notes: AUB: abnormal uterine bleeding.

Rationale

The hormonal therapies available to reduce or stop AUB are the LNG-IUS, oral progestogens, COC, and GnRHa. The LNG-IUS is effective for AUB (all causes combined) in 90% of cases [54]. It has no effect on fibroid volume. Type 0–1 fibroids can impede the IUS placement and promote spontaneous expulsions. While GnRHa is equally effective, it has important side effects (including but not limited to hot flushes and osteoporosis) that prevent any recommendation for its long-term use [107].

Hysteroscopic myomectomy is the reference treatment for type 0–2 fibroids. It effectively treats AUB in women with a normal-size uterus [108]. Its operative time, length of stay, and convalescence are short, and it enables an early return to work. Hysteroscopic myomectomies lead to stopping AUB in 70% of cases with a two-year follow-up and prevent recurrence in more than 90% of cases [109]. The very low complication rate is acceptable.

The only study related to this question compared the effectiveness of the LNG-IUS to that of thermal endometrial balloon ablation in women with AUB associated with type 1–2 fibroids < 5 cm, in women not considering pregnancy [110]. Both techniques were effective for reducing bleeding (reduction of PBAC: 345 ± 42 vs 338 ± 47), improved the haemoglobin level (2.6 ± 0.9 vs. 3.0 ± 1.0), and yielded a high satisfaction rate (78% vs 88%), with no significant differences between methods.

Overall, oral hormonal therapies, the LNG-IUS, and hysteroscopic myomectomy are effective and well tolerated for treating AUB. In the absence of a comparative study, there is no evidence justifying a preference for one or another of these treatments.

PICO 21: In women with AUB associated with one or more type 0–2 fibroids and no immediate desire to become pregnant, is a hormonal therapy prescribed as first-line treatment associated with a reduction in the use of hysteroscopic myomectomy?

No Recommendation

Rationale

The data in the literature are currently insufficient to answer this question. Studies about the interest of a GnRHa treatment before hysteroscopic resection of submucosal fibroids to simplify the procedure are available, but none aimed at reducing the surgery rate.

In women with AUB associated with one or more type 0–2 fibroids and no immediate desire for pregnancy, no evidence supports the prescription of hormonal treatment as a first-line treatment to reduce the use of hysteroscopic myomectomy.

PICO 22: In women with AUB associated with one or more type 0–2 fibroids and planning a pregnancy, is hysteroscopic myomectomy more effective than antigonadotropic hormonal therapies for treating AUB and becoming pregnant?

R5.1 – A hysteroscopic myomectomy is suggested for treating women with AUB associated with one or more type 0–2 fibroids and planning an immediate pregnancy.

Weak recommendation, Low quality of evidence.

Rationale

Type 0–2 fibroids have a negative impact on spontaneous fertility and their surgical treatment has uncertain consequences on fertility as well [111,112]. Overall, oral antigonadotropic therapies, the LNG-IUS, and hysteroscopic myomectomy are effective and well tolerated for treating AUB. Only hysteroscopic myomectomy, however, is compatible with a plan for immediate pregnancy.

A randomized controlled study compared hysteroscopic myomectomy to expectant treatment in infertile women with a single type 0–2 fibroid < 40 mm (bleeding profile not described): the conclusions favoured the myomectomy for becoming pregnant within 1 year: 13/30 (43%) vs 6/22 (27%) [113]. Nonetheless a supplementary analysis of the study performed by the Cochrane collaboration concluded that the difference was not significant: OR 2.0; 95% CI 0.6, 6.7 [114]. A single prospective randomized study compared the onset of pregnancy after hormonal therapy by GnRHa (3/5, 60%) to hysteroscopic myomectomy (1/5, 20%) [115]. The small sample (10 women) did not allow a significant difference to be detected.

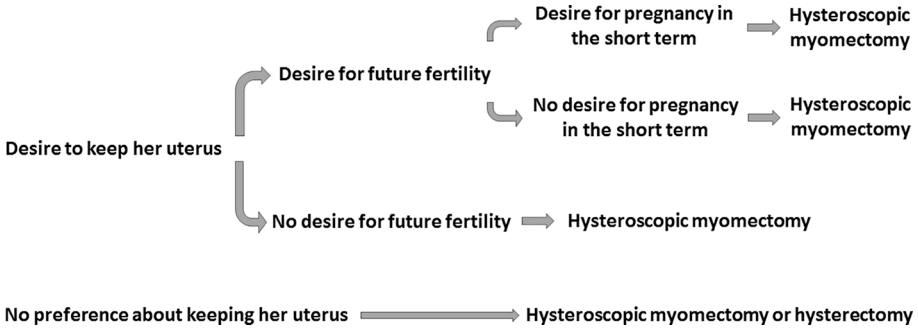

Fig. 4. Decision tree for treatment of women with AUB and fibroids type 0–2. Notes: AUB: abnormal uterine bleeding.

PICO 23: In women with AUB associated with one or more type 0–2 fibroids who are considering surgery, is hysteroscopic myomectomy superior to hysterectomy for treating AUB and improving QoL?

No Recommendation

Rationale

Hysteroscopic myomectomies have been shown to stop AUB in 70% of cases with a two-year follow-up and prevent recurrence in more than 90% of cases [108,109]. Its short operative time, length of stay, and convalescence enable an early return to work. Hysterectomy resolves AUB in all cases and improves QoL. Minimally invasive routes must be preferred over laparotomy to reduce complications and improve QoL in the short term [75]. The complication rates are low for both techniques (<5%), but higher and possibly more serious for hysterectomy [116].

In a prospective non-randomized study comparing myomectomy to hysterectomy in a population of 167 women, fibroid-related QoL (UFS-QoL) at one year was better after hysterectomy than myomectomy [117]. The comprehensive QoL (SF-36) and adverse effects (13%) were similar in the two groups. Nonetheless, the women did not have only AUB and only 44% of those in the myomectomy group had had a hysteroscopic resection of a fibroid, probably type 0–2. There were no subgroup analyses of these women.

Overall, in women with AUB associated with one or more type 0–2 fibroids and for which an intervention is planned, there is no evidence supporting a preference for either a hysteroscopic myomectomy or a hysterectomy for treating AUB and improving QoL. The information about the effectiveness and surgical risks of these two techniques, and especially the woman's desire to keep her uterus or not provide a basis allowing women to choose.

PICO 24: In women with AUB associated with one or more type 0–2 fibroids and who are going to have a hysteroscopic myomectomy, would preoperative treatment by a GnRHa help to facilitate the surgical procedure?

No Recommendation

Rationale

Treatment by GnRHa induces both AUB reduction and a decrease in fibroid size. It is authorized for a duration of 3 months in preparation for gynaecological surgery, including myomectomies, regardless of the approach.

Three randomized trials have compared GnRHa treatment followed by hysteroscopic resection to hysteroscopic resection only for women with symptomatic type 0–2 fibroids. Their results were discordant:

1) One favoured the GnRHa treatment for reducing operative time (by 7 min) and fluid absorption (by 200 mL) for a single type 0 or 1 fibroid <35 mm in diameter [118];
2) Another found GnRHa treatment less favourable, with a longer operative time (by 6 min) and a higher proportion of incomplete resections, especially for type 2 fibroids [119];
3) The third found no significant difference in the rates of complete resection, operating time, and fluid absorption for type 1 and 2 fibroids [120].

The results of a non-randomized study favoured the preoperative use of GnRHa for operative time and fluid absorption [121]. A retrospective study showed no difference between these options, except for a longer operative time for the GnRHa pretreatment [109]. Moreover all of these studies reported very low complication rates, regardless of the treatment option chosen.

Overall, for women with AUB associated with one or more type 0–2 fibroids with hysteroscopic resection planned, the discordant data from the literature do not provide any evidence justifying preoperative GnRHa treatment intended to facilitate the surgical procedure.

Domain 6: Type 3 (or a higher type) fibroids (Fig. 5)

PICO 25: In women with AUB associated with one or more type 3 (or higher) fibroids, are hormonal treatments effective and well tolerated for treating AUB, reducing the surgery rate, or modifying the surgical approach?

R6.1 – In women with AUB associated with one or more type 3 (or higher) fibroids < 10 cm who have anaemia and a planned hysterectomy, we recommend treatment by GnRHa for 3 months to improve preoperative blood haemoglobin before surgery.

Strong recommendation, Low quality of evidence.

R6.2 – In women with AUB associated with one or more type 3 (or higher) fibroids < 10 cm and a planned hysterectomy, we suggest treatment by GnRHa for 3 months to reduce the laparotomy rate and facilitate the surgery.

Weak recommendation, Low quality of evidence.

R6.3 – In women with AUB associated with a uterus of average size and one or more type 3 (or higher) fibroids who want contraception, insertion of an LNG-IUS (52 mg) is recommended (in the absence of contraindications).

Strong recommendation, Moderate quality of evidence.

Rationale

Data from the literature have compared GnRHa with placebo or with UPA and assessed the interest of other SPRMs and of the LNG-IUS among women who did not want a pregnancy in the short term and who had AUB associated with one or more type 3 (or higher) fibroids:

1) GnRHa vs placebo: among women treated with GnRHa preoperatively for 3 months, the pre- and postoperative (+0.85 g/dL, $P = 0.002$) haemoglobin levels rose significantly, while significant reductions were observed in the hysterectomy rate (OR 0.34; 95% CI 0.21, 0.54; $P < 0.001$), operative time (-10 min; 95% CI −17,-3; $P = 0.004$), and difficulties with the hysterectomy, all approaches combined [81]. No impact of the approach for the myomectomy was observed.
2) GnRHa vs UPA: among women with a uterus of average size with type 2 (or higher) fibroids from 3 to 10 cm in diameter, no significant differences were observed between GnRHa and UPA for improvement in bleeding scores, amenorrhoea, or QoL [122]. Nonetheless, the effectiveness of GnRHa on the reduction of uterine volume was greater than that of UPA. The literature does not allow us to reach a conclusion about the impact of GnRHa on the surgery rate, since it was studied for presurgical aims. Nonetheless, approximately 45% of the women declined surgery after 12 weeks of treatment regardless of the preoperative treatment used [122]. A similar renunciation rate (42%) for surgery has been reported at 1 year after 3 months of UPA treatment [123]. Nonetheless, the withdrawal of UPA from the market due to its hepatotoxicity no longer allows its recommendation.
3) Other SPRMs: the effectiveness of vilaprisan was compared with that of placebo in women with AUB associated with type 2 (or higher) fibroids from 3 to 10 cm in diameter [124]. Vilaprisan was more effective than placebo for the control of AUB and for eliminating bleeding completely at 12 weeks in nearly 60% of cases. Nonetheless, as this substance was not marketed in France in 2022, we cannot recommend it.
4) LNG-IUS: the effectiveness and tolerability of this device have been evaluated in non-comparative cohort studies of women with AUB in

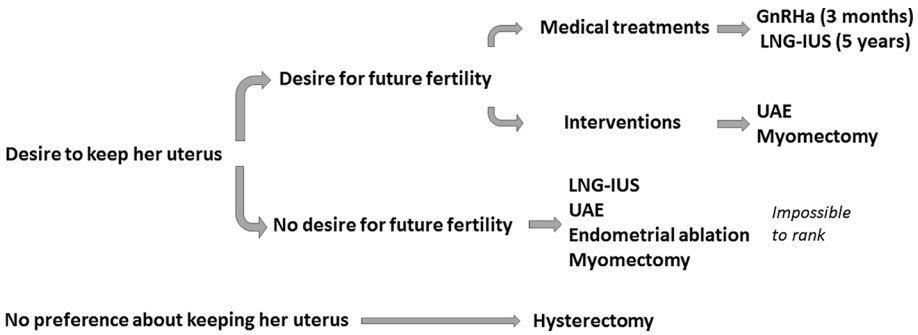

Fig. 5. Decision tree for treatment of women with AUB and fibroids type 3 and higher. Notes: AUB: abnormal uterine bleeding; LNG-IUS: levonorgestrel intra-uterine system 52 mg; GnRHa: GnRH analogues; UAE: uterine artery embolization.

a uterus of average size with one or more type 3 (or higher) fibroids. The bleeding scores and haemoglobin levels improved significantly over time [125–127]. In women referred for hysterectomy and agreeing to LNG-IUS insertion as an alternative, the rate of surgery at 12 months was 21%, and 50% continued with the LNG-IUS [127]. A literature review found a hysterectomy rate of 3% to 25% between 3 and 12 months after device insertion, without information about the patients' desire to keep their uterus [125]. The causes were device expulsion, persistent AUB, and abdominal pain. No study has looked at the impact of the LNG-IUS on modifying the surgical approach. Studies about its impact on the volume of either the uterus or the fibroids are discordant. In a randomized trial comparing the LNG-IUS to a COC, the reduction of AUB and increased haemoglobin level favoured the LNG-IUS [128]. The adverse effects reported were spotting, breast tenderness (6% to 31%), weight gain (10% to 18%), headaches (6% to 12%), and device expulsion (6% to 12%). Only device expulsion was a motive for stopping its use [124].

Addendum (2023)

Elagolix and relugolix are orally bioavailable, second-generation, non-peptide GnRH antagonist, given in combination with estradiol/norethindrone acetate for the management of AUB associated with uterine fibroid in premenopausal women up to 24 months. Add-back therapy given with GnRH antagonist decreases vasomotor symptoms and bone mineral density loss. Randomized trials named ELARIS and LIBERTY compared the efficacy of elagolix and relugolix to placebo after 6 to 12 months of treatment. All showed a significant reduction in menstrual bleeding in 76% to 88% of patients. In the extended study on relugolix, with a treatment period of 76 weeks, 88% of the patients reached the end goal of mean blood loss < 80 mL and greater than 50% reduction of blood loss from the baseline. Both elagolix and relugolix are generally well tolerated, and most patients have mild to moderate adverse effects, such as headaches, hot flushes, night sweats, and vaginal dryness. The duration of use is limited to 24 months for the increased risk of irreversible bone mineral density loss associated with prolonged use. Following discontinuation, hormonal levels return rapidly to normal values along with restoration of menstruation. This represents an advantage for women pursuing future fertility, but also exposes them to a risk of recurrence.

PICO 26: In women who have AUB associated with one or more type 3 (or higher) fibroids and no immediate desire for pregnancy, are hormonal treatments more effective and better tolerated than surgical treatments for treating AUB?

No Recommendation

Rationale

Among the hormonal treatments, GnRHa as a monthly injection prescribed for 3 months reduces the size of the fibroids and improves the preoperative haemoglobinaemia [81]. The LNG-IUS is effective and well tolerated for treating AUB and reduces the rate of surgery [125].

Among the surgical treatments, hysterectomy is the most effective in treating AUB, but its morbidity is greater than that of endometrial ablation [129]. The hysterectomy rate for recurrence after endometrial thermocoagulation is 5% [130]. Although myomectomy is effective, it exposes women to a risk of recurrence ranging from 27% to 62% at 5 to 10 years, with a risk of reintervention on the order of 17% [131]. The morbidity of myomectomy and hysterectomy by laparotomy are similar.

No study has compared hormonal to surgical treatment in women with AUB associated with one or more type 3 (or higher) fibroids.

Overall, for women with AUB associated with one or more type 3 (or higher) fibroids, the LNG-IUS, which is the only hormonal treatment that can be prescribed on a long-term basis, and surgical treatment (endometrial ablation, myomectomy, hysterectomy) are effective and well tolerated for treating AUB.

The absence of comparative data between hormonal therapies (the LNG-IUS) and surgical treatment means that there is no evidence to support a preference for one of these strategies over the other. The choice will be guided by the clinical criteria and the patient's wishes.

PICO 27: In women with AUB associated with one or more type 3 (or higher) fibroids, who are considering surgery and no longer desire future fertility, is hysterectomy more effective and better tolerated than the conservative surgical treatments for treating AUB?

R6.4 – Endometrial ablation is suggested for a woman with AUB and a uterus of average size (hysterometry $\leq$ 12 cm) and one or more type 3 (or higher) fibroids, who is considering surgery and desires to keep her uterus (but not her fertility).

Weak recommendation, Moderate quality of evidence.

R6.5 – A hysterectomy by a laparoscopic or vaginal route is recommended for a woman with AUB associated with one or more fibroids of type 3 (or more) who is considering surgery and does not want to keep her uterus.

Strong recommendation, Low quality of evidence.

Rationale

Hysterectomy is the most effective method for treating AUB because it ends bleeding in 100% of cases [75,129,132]. When performed by a minimally-invasive approach, it enables the best improvement in QoL and permits patients to have a better perception of their physical and psychological health status in the short term than does the myomectomy [133]. When performed by laparotomy, hysterectomy does not differ from myomectomy in terms of perioperative morbidity and short term QoL. Myomectomy exposes women to a risk of recurrence ranging from 27% to 62% at 5 to 10 years, with a risk of reintervention on the order of 17% [131,134]. The techniques of endometrial resection or

ablation are effective treatments that are well tolerated for treating AUB [67].

A single study has compared endometrial thermocoagulation and vaginal hysterectomies among women with type 3 (or higher) fibroids and an average-sized uterus (hysterometry < 12 cm) [130]. Endometrial thermocoagulation results in amenorrhoea or hypomenorrhoea in 95% of cases at 24 months. Operative time, postoperative pain, length of stay, and blood loss are all lower after thermocoagulation than after a vaginal hysterectomy. Both techniques improve QoL, but in the short term (6 months), the improvement is greater after hysterectomy.

Overall, a myomectomy can be proposed to a woman with a very large uterus that she wants to keep, after she has been informed of the risks of recurrence and of a subsequent hysterectomy. Endometrial ablation by thermocoagulation can be proposed to a woman who wants to keep her averaged-sized uterus with one or more type 3 (or higher) fibroids. Endometrial resection has not been studied in this population, but can be chosen in the absence of any significant difference between techniques of the first and second generation in other indications.

PICO 28: In women with AUB associated with one or more type 2–6 fibroids, are interventional radiology techniques more effective and better tolerated than medical treatments for treating AUB?

No Recommendation

Rationale

UAE is an interventional radiology technique requiring technical equipment, appropriate facilities, and a hospital stay. A meta-analysis reported an effectiveness of 85% for curing AUB associated with fibroids at 2 years, a satisfaction rate of 85%, and a 14% rate of secondary surgery for all causes combined [135]. Its perioperative tolerability is better than all the surgical options, even minimally-invasive surgery [135–137].

The technique of high intensity focused ultrasound (HIFU) can be combined with MRI or ultrasound; its reduced accessibility — available only at a single centre in France in 2022 — limits its widespread use. In a meta-analysis of 16 trials including one comparing HIFU and placebo, HIFU reduced the symptoms associated with fibroids; its effectiveness against AUB was 69% [138]. Nonetheless, a comparative study showed an increase in the risk of reinterventions after HIFU compared with UAE [139].

Among the non-hormonal medications, the NSAIDs and tranexamic acid are given as first-line treatment [140]. NSAIDs reduce the production of prostaglandins and improve AUB in comparison with placebo [141,142]. Tranexamic acid is more effective than NSAIDs for AUB, but no specific studies of good quality have examined it with type 2–6 fibroids [141,142].

Among the hormonal treatments, GnRHa, prescribed for 3 months, reduces the size of fibroids and improves preoperative haemoglobinaemia [140]. The LNG-IUS is effective and well tolerated for treating AUB and reduces the surgery rate [143].

The literature contains no study comparing UAE or HIFU with a medical treatment to assess their relative effectiveness, except for a meta-analysis [144]. It collected the results of 4 Chinese studies comparing HIFU with mifepristone – none with full texts in English. The rate of partial or total necrosis of fibroids is better after HIFU than mifepristone (OR 5.9; 95% CI 2.9, 11.7; $P < 0.01$), with a trend toward fewer gastrointestinal adverse effects (OR 0.07; 95% CI 0, 1.35).

Overall, interventional radiology techniques (UAE and HIFU) and medication are effective and well tolerated for treating women with AUB associated with one or more type 2–6 fibroids. The data in the literature are insufficient to justify a recommendation preferring any particular treatment strategy.

PICO 29. In women with AUB associated with one or more type 2–6 fibroids, are interventional radiology techniques more effective and better tolerated than myomectomy for treating AUB?

R6.6 – A woman with AUB associated with one or more type 2–6 fibroids, who desires to keep her uterus, and for whom an intervention is indicated, should be offered a choice of UAE or myomectomy and should be informed of the better postoperative tolerability and increased risk of reinterventions in the long term after UAE.

Strong recommendation, Moderate quality of evidence.

R6.7 – We suggest that women with AUB associated with one or more type 2–6 fibroids, who consider pregnancy, and for whom an intervention is indicated, be offered a choice of a myomectomy or UAE, and that they be informed of the uncertainties about subsequent fertility and of the risk of miscarriage after UAE.

Weak recommendation, Low quality of evidence.

Rationale

1) UAE vs myomectomy: the literature contains randomized trials, sometimes grouped in meta-analyses, comparing interventional radiology and myomectomy in non-menopausal women with symptomatic fibroids exceeding 4 cm [135,136,145,146]. The duration of hospitalization and convalescence are both shorter after UAE than after myomectomy [145,146]. QoL indices favour myomectomy at 6, 12, and 24 months [135,145]. Symptom scores, like the bleeding score, are significantly higher at 6 months after UAE, while the differences are no longer significant at 12 or 24 months. The risk of reintervention is significantly higher two years after UAE, with variable rates between the different series [135,136,145,146]. In a randomized study after 2 years of follow-up, 84% of patients said they would recommend UAE to a friend and 93% myomectomy, and 74% and 78% respectively said they would undergo the same intervention again [145]. In terms of fertility, the markers of ovarian reserve (AMH, FSH, LH) are not impaired relative to control patients after either UAE or myomectomy [145,147]. Compared with UAE, myomectomy is associated with higher ongoing pregnancy rates (78% vs 50%), lower miscarriage rates (23% vs 64%), and better live-birth rates (48% vs 19%) [146]. A meta-analysis including the preceding study found only an increased risk of miscarriages after UAE, but no difference in pregnancy rates [148].
2) HIFU vs myomectomy: there are no studies comparing HIFU with myomectomy for patients with a symptomatic fibromatous uterus. A meta-analysis of Chinese studies, most with their full-text in Chinese, shows no difference in effectiveness between myomectomy or hysterectomy and HIFU: 0.6%, OR 0.3; 95% CI 1, 4) [144].

PICO 30. In women with AUB associated with one or more type 2–6 fibroids, who are considering surgery and no desire future fertility, is hysterectomy more effective and better tolerated than interventional radiology techniques for AUB?

R6.8 – Women with AUB associated with one or more type 2–6 fibroids and considering a hysterectomy should be offered a choice of UAE or hysterectomy and should be informed of the better postoperative tolerability and increased risk of reinterventions in the long term after UAE.

Strong recommendation, Moderate quality of evidence.

Rationale

1) Hysterectomy vs UAE: three randomized trials comparing UAE to hysterectomy in women with a symptomatic fibroid uterus with AUB (2 trials) were included in a meta-analysis [135,149–151]. UAE was accompanied by more technical failures than hysterectomy, but the

increase in the risk of reintervention due to these failures was not significant [135]. The major complication rate was similar in both groups. Nonetheless, the risk of transfusion was 20 times higher after hysterectomy than UAE, and the minor complications were significantly more frequent with UAE. The duration of hospitalization and convalescence were significantly shorter after UAE. The frequency of complete symptom regression was similar for these two procedures. After 1 and 2 years, resolution of AUB by UAE appears significantly less frequent, although the amplitude of the effect is moderate. Globally patients treated by UAE had a risk of reintervention 3 times higher than those with hysterectomies, independently of technical failures, particularly for persistence of symptoms after 2 and 5 years. Women's satisfaction at 2 years was similar for hysterectomy and UAE. Nonetheless, the women reported that they would recommend hysterectomy to a friend slightly but significantly more often than UAE [135].

2) Hysterectomy vs HIFU: No studies compare HIFU with hysterectomy in the context of a symptomatic fibroid uterus. A meta-analysis of Chinese studies, most with their full-text in Chinese, shows no difference in effectiveness between myomectomy/hysterectomy and HIFU: 0.6%, OR 0.3; 95% CI 1, 4 [152].

Domain 7: Adenomyosis (Fig. 6)

PICO 31: In women with AUB associated with adenomyosis, is the LNG-IUS more effective and better tolerated than the other hormonal therapies for treating AUB?

R7.1 – We suggest that the LNG-IUS (52 mg) be preferred (in the absence of contraindications) over COC for women with AUB associated with adenomyosis and requiring medical treatment.

Weak recommendation, Moderate quality of evidence.

Rationale

A single published study has compared the LNG-IUS to a third-generation COC (30 μg ethinyloestradiol and gestodene) in women with AUB associated with adenomyosis. The improvement in the bleeding profile is superior for women treated by the LNG-IUS, compared with those treated by COC; the mean number of days of bleeding at 6 months were respectively 2.6 ± 2.1 and 5.2 ± 1 [153].

The other combined contraceptives (oral, vaginal, or transdermal), progestogen treatment (oral, implant, MPA, or dienogest), and GnRHa have not been compared with the LNG-IUS, or with each other, for the treatment of AUB associated with adenomyosis.

PICO 32: In women with AUB associated with adenomyosis, is the combination of conservative surgical treatment and hormonal therapy more effective and better tolerated than either conservative surgical treatment or hormonal therapy alone for treating AUB?

R7.2 – We suggest that endometrial resection or ablation be combined with hormonal therapy for women with AUB associated with adenomyosis who require conservative surgical treatment and have no desire for future fertility.

Weak recommendation, Low quality of evidence.

Rationale

Conservative surgical treatment (endometrial resection or ablation) and hormonal therapies (GnRHa, LNG-IUS, COC) are effective and well tolerated for treating AUB associated with adenomyosis. Nonetheless, no study in the literature has compared them. Several studies have however compared the effectiveness of conservative surgical treatment (endometrial resection) combined with hormonal therapies (GnRHa pre-resection, LNG-IUS post-resection) to that of surgical or hormonal treatment alone for AUB with adenomyosis [154–156]. The results favour the combination of surgical treatment with hormonal therapies: increased rate of amenorrhoea at 1 year (100% vs 9%–16%), diminution of repeat surgery (0% vs 19%), and absence of difference in the occurrence of complications or adverse effects.

One study shows that for the treatment of adenomyosis the combination of postoperative hormonal treatment by GnRHa with conservative surgical treatment (adenomyomectomy) improves effectiveness and tolerability compared with surgical treatment only [157].

PICO 33: In women with AUB associated with adenomyosis, is hysterectomy more effective and better tolerated than hormonal therapies for treating AUB?

R7.3 – We suggest that hormonal therapy by LNG-IUS (52 mg) (in the absence of contraindications) be proposed as a first-line treatment for women with AUB associated with adenomyosis, for the purpose of improving some aspects of QoL and of reducing postoperative morbidity after a hysterectomy.

Weak recommendation, Low quality of evidence.

Rationale

A single published study has compared hysterectomy with the LNG-IUS in women with AUB associated with adenomyosis [158]. The augmentation in the haemoglobin concentration with the LNG-IUS appears similar to that obtained with a hysterectomy. The improvement in the bleeding profile was superior among women treated by hysterectomy: 100% vs 51% of amenorrhoea at 1 year. Nonetheless, the QoL evaluation tended to be best with the use of the LNG-IUS at 1 year for some criteria, especially for psychological and social well-being. The risk of surgery if initial medical treatment failed was low (2%) and associated with the spontaneous expulsion of the device. The risk of postoperative complications of hysterectomy was 4% in this study [158].

The other combined contraceptives (oral, vaginal, or transdermal), progestogen treatment (oral, implant, MPA, or dienogest), and GnRHa have not been compared with hysterectomy for the treatment of AUB associated with adenomyosis.

PICO 34: In women with AUB associated with adenomyosis and considering surgery, is hysterectomy more effective and better tolerated than conservative surgical treatments for AUB?

R7.4 – A woman with AUB associated with adenomyosis who is considering surgery and desires to keep her uterus should be offered endometrial resection or ablation, but she should be informed of the risk of failure and the ensuing need for a subsequent hysterectomy.

Strong recommendation, Low quality of evidence.

R7.5 – A hysterectomy by a laparoscopic or vaginal route should be offered to a woman with AUB associated with adenomyosis with surgery planned and no preference about keeping her uterus, to reduce the risk for repeat surgery for recurrent AUB.

Strong recommendation, Low quality of evidence.

Rationale

AUB attributed to adenomyosis and eligible for an intervention can be treated by surgery — either conservative (endometrial resection or ablation) or radical (hysterectomy). In idiopathic AUB, the techniques for endometrial resection or ablation, compared with hysterectomy, are associated with a shorter operative time, hospitalization, and convalescence, as well as an earlier return to work. These results can be transposed to women with adenomyosis. Nonetheless, the risk of failure

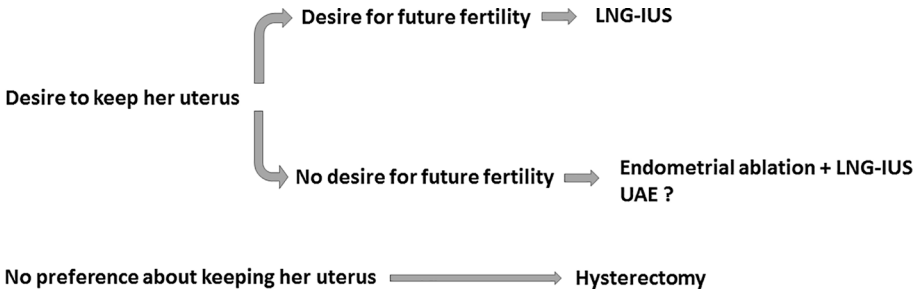

Fig. 6. Decision tree for treatment of women with AUB and adenomyosis. Notes: AUB: abnormal uterine bleeding; LNG-IUS: levonorgestrel intra-uterine system 52 mg; UAE: uterine artery embolization.

of conservative treatments is greater when adenomyosis is present. The data from the literature, although heterogeneous and derived from small series, finds moderate symptom improvement and AUB recurrence rates that can require a subsequent hysterectomy of 10% to 70% [159–165]. Hysterectomy is therefore an integral part of the treatments to be discussed and proposed to women with AUB associated with adenomyosis. The risk of postoperative complications (infection, pelvic or parietal haematoma, transfusion) is higher among women treated by hysterectomy and thus must be discussed in the light of each woman's history.

Overall, for women with AUB associated with adenomyosis, the absence of comparative studies makes it impossible to prefer any one of an endometrial resection or ablation or a hysterectomy or vice versa. The treatment choice will be based principally on the woman's desire to keep her uterus and her comorbidities.

PICO 35: In women with AUB associated with adenomyosis, are interventional radiology techniques more effective and better tolerated than medical treatments for AUB?

No Recommendation

Rationale

Among the non-hormonal treatments, tranexamic acid is more effective than NSAIDs for treating AUB, but there are no data specific for adenomyosis [141,166]. Among the hormonal therapies, the LNG-IUS reduces blood loss and uterine size: standardized mean difference −2.32, 95% CI −2.91, −1.73, $P < 0.001$, for PBAC up to 36 months after LNG-IUS insertion [167]. Dienogest shows a reduction in adenomyosis-associated pain compared with placebo at 4 months, but there are no data concerning effectiveness for AUB [168]. SPRMs are effective for the reduction of AUB at three months after treatment (95% for UPA vs 0% for placebo, $P < 0.01$), but this difference disappears three months after treatment stops (25% for UPA vs 0% (placebo), $P = 0.54$) [169]. Moreover, UPA has been removed from the market due to serious adverse effects by hepatotoxicity. The effectiveness of GnRHa is counterbalanced by the limitation of the duration of their prescription due to their side effects [166]. The anti-aromatases are as effective as GnRHa in reducing uterine volume and adenomyosis at three months, as well as in decreasing menometrorrhagia in a subgroup of symptomatic women (4/9 (44%) vs 10/11 (91%), NS) [170]. The absence of any marketing authorization in this indication does not allow us to make any recommendations.

UAE has been considered a minimally invasive treatment for symptomatic uterine fibroids since 1995. This procedure is effective and well tolerated, as long as it includes a hospitalization of 12–24 h for the management of immediate post-operative pain. The indication has been extended to adenomyosis. The cumulative success rate based on standardized questionnaires, but not specifically on AUB, is 80% at long term (4 to 7 years), with 18% of women requiring secondary hysterectomy [171,172]. A systematic review and meta-analysis of HIFU treatment for adenomyosis shows a significant reduction in dysmenorrhoea and improvement in quality of life at 12 months [173]. However, the findings of the meta-analysis are based on fewer and heterogeneous studies, data on AUB are lacking, and no trials comparing the HIFU technique to other conservative treatments are available.

Overall, in women with AUB associated with adenomyosis, both medical treatments and interventional radiology techniques appear effective and well tolerated. The absence of comparative studies prevents any recommendation preferring either of these types of treatment over the other for women, regardless of whether or not they desire future fertility.

PICO 36: In women with AUB associated with adenomyosis, are interventional radiology techniques more effective and better tolerated than conservative surgical treatment for AUB?

No Recommendation

Rationale

UAE is effective and well tolerated in women with symptomatic adenomyosis; its cumulative success rate, based on standardized questionnaires but not specifically on AUB, is 80% at long term (4 to 7 years), with 18% of women requiring secondary hysterectomy [171,172]. HIFU is also effective in adenomyosis, significantly reducing dysmenorrhoea and improving quality of life at 12 months [173]. Adverse reactions after HIFU are reported in 56% of patients. However, the findings of the meta-analysis are based on fewer and heterogeneous studies, data on AUB are lacking, and no trials comparing the HIFU technique with other conservative treatments are available.

Adenomyosis has long been considered a factor for failure in first-generation techniques of endometrial resection. This risk appears to be lower with the second-generation [174,175]. In a study of 43 women (37 with heavy menstrual bleeding) treated by RFA for adenomyosis, the bleeding score was normalized in 93% of women at six months and 86% at three years [165]. These techniques are contraindicated for women who wish to become pregnant. Other surgical methods are described in the literature, such as partial or total metrectomies (or cytoreduction); the principal problem is their reproducibility and their learning curve. Few studies have examined the risks of short- and long-term complications of these techniques, especially their impact on fertility [176–178].

Overall, in women with AUB associated with adenomyosis, interventional radiology and conservative surgery appear effective and well tolerated. The absence of comparative studies prevents any recommendation preferring either technique over the other, regardless of their desire for future fertility.

PICO 37: In woman with AUB associated with adenomyosis, is hysterectomy more effective and better tolerated than interventional radiology techniques for treating AUB?

No Recommendation

Rationale

Hysterectomy is considered the reference treatment for symptomatic adenomyosis, initially or after conservative treatments have failed [179].

Hysterectomy is very effective for treating AUB, but exposes women to the risks of intraoperative visceral injuries and long-term complications, such as pelvic-abdominal pain, urinary dysfunction, bowel dysfunction, pelvic floor conditions, and sexual dysfunction [116].

UAE is effective and well tolerated in women with symptomatic adenomyosis; its cumulative success rate, based on standardized questionnaires but not specifically on AUB, is 80% in the long term (4 to 7 years), with 18% of women requiring secondary hysterectomy [171,172]. Its perioperative tolerability is better than all the surgical options, even minimally invasive surgery. A randomized study comparing UAE to hysterectomy among women with adenomyosis is underway in the Netherlands (the QUESTA trial) [180]. Its results are not yet available.

HIFU is a technique that can be combined with MRI or ultrasound [181]. Its reduced accessibility — available at only one centre in France in 2022 — limits its widespread use. A retrospective medical-economic study comparing hysterectomy to HIFU in symptomatic adenomyosis showed identical and significant improvement in QoL in both groups and a lower cost for HIFU [181].

Overall, in women with AUB associated with adenomyosis, interventional radiology techniques and hysterectomy appear effective and well tolerated. The absence of comparative studies prevents any recommendation preferring either technique over the other for women, regardless of whether or not they desire future fertility.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Matthias Barral has been invited to a congress in 2019 by Guerbet. Jean-Luc Brun has been a member of the Gedeon Richter board until 2019. He has been a speaker for Ipsen in 2018 and Bayer in 2019. Pauline Chauvet has been a speaker for Gedeon Richter in 2018 and 2019. Marion Cortet has been invited to a congress in 2019 by Roche. Gil Dubernard has been a member of the Hologic board and organized a symposium for Hologic in 2018 and 2019. Géraldine Giraudet has been a member of the Gedeon Richter board since 2016. She has been a consultant for Boston Scientific since 2017. She has been carried out training sessions for AMI and Olympus since 2018 and participated to symposium for Applied in 2019. Olivier Graesslin has been a member of the Gedeon Richter board until 2019, and the MSD board until 2018. He has been a speaker for Bayer until 2019 and for MSD between 2016 à 2018. Cyrille Huchon has been a speaker for Gedeon Richter from 2012 to 2019. He has been invited to congresses by Nordic Pharma from 2014 to 2019. He has been a speaker for Astra Zeneca in 2017. He has been a consultant for A+A, Icomed, M3 Global Research Ltd and WorldOne Group B.V. from 2012 to 2019, and for the society Ziwig since 2020. Justine Hugon Rodin has been a speaker for Effik in 2019. Guillaume Legendre has been chairing scientific meetings for Gedeon Richter and Bayer Healthcare from 2018 to 2020. Lorraine Maitrot Mantelet has been a speaker for Astra Zeneca in 2015 and 2019, Effik in 2019 and Ferring in 2015 and 2018. She has been invited to congresses by Bayer in 2015 and 2016, Besins in 2019 and Gedeon Richter since 2016. She had signed hospitality agreement with Mithra in 2019, MSD in 2015 and 2016, Nordic Pharma in 2015 and 2018 and Roche in 2015 and 2016. Louis Marcellin has been a speaker for Ipsen in 2020. Henri Marret has been a member of the Gedeon Richter board until 2019. Thibault Thubert has been a consultant for Pierre Fabre in 2019 and Pileje in 2020. Antoine Torre has been invited to congresses by Guerbet in 2019 and 2020. Florence Trémollières has been a consultant for Theramex in 2018. She has been a speaker for Theramex, Arrow and Amgen in 2018 and 2019. She has been invited to a congress by Besins Healthcare in 2018. Hélène Vernhet-Kovacsik has been a consultant for the société Télédiag until 2017. She has been a speaker for General Electric and Guerbet in 2021. None, for Xavier Ah-Kit, François Cornelis, Patrice Crochet, Victoire Delporte, Anna Gosset, Lise Lecointre, Laura Miquel, Marine Le Mitouard, Geneviève Plu-Bureau, Claire Proust, Alix Roquette, Pascal Rousset, Eva Sangnier, Marc Sapoval, and Fabien Vidal.

Acknowledgments to the reviewers

Yves Aubard (G, Limoges, public), Michaël Ayeva Derman (G, Nantes, private), Valérie Bernard (G, Bordeaux, public), Sandrine Brugère (G, Bordeaux, private), Perrine Capmas (G, Bicêtre, public), Nathalie Chabbert-Buffet (G, Paris, public), Elisabeth Chéreau Ewald (G, Marseille, private), Ludovic Cravello (G, Marseille, public), Hélène Creux (G, Montpellier, private), Sabrina Da Costa (G, Paris, public), Lise Duranteau (G, Bicêtre, public), Jean-Philippe Estrade (G, Marseille, private), Hervé Fernandez (G, Bicêtre, public), Xavier Fritel (G, Poitiers, public), Olivier Garbin (G, Strasbourg, public), Tristan Gauthier (G, Limoges, public), Hélène Gbaguidi (G, Orléans, public), Anne Gompel (G, Paris, public), Virginie Grouthier (G, Bordeaux, public), Thomas Hébert (G, Tours, public), Claude Hocké (G, Bordeaux, public), Martin Koskas (G, Paris, public), Pénélope Labauge (R, Versailles, public), Vincent Lavoué (G, Rennes, public), Brigitte Letombe (G, Lille, private), Jean Levêque (G, Rennes, public), Julia Maruani (G, Marseille, private), Angèle Mbarga (PA, Fibrome Info France), Stéphanie Mignot (GP, Poitiers, private), Camille Mimoun (G, Paris, public), Elisabeth Paganelli (G, Tours, private), Catherine Pienkowski (P, Toulouse, public), Rajeev Ramanah (G, Besançon, public), Emmanuelle de Raucourt (H, Beaujon, public), Pia de Reilhac (G, Nantes, private), Geoffroy Robin (G, Lille, public), Etienne Roussel (G, Blois, public), Olivier Serres-Cousiné (R, Montpellier, private), Catherine Ternisien (H, Nantes, public), Sabine Trebaol (PA, EndoFrance), Estelle Wafo (G, Marne-la-Vallée, public).

* G: gynecologist; GP: general practionner; H: hematologist; P: pediatrician; PA: patient association; R: radiologist/City/setting.

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