Review

Women's Health

Surgical management of abnormal uterine bleeding in fertile age women

Abnormal uterine bleeding is a common gynecological disease and represents one of the most frequent reasons for hospital admission to a specialist unit, often requiring further surgical treatment. Following the so-called PALM-COEIN system we will attempt to further clarify the surgical treatments available today. The first group (PALM) is characterized by structural lesions, which may be more appropriately treated by means of surgical management. Although hysterectomy remains the definitive and decisive choice, there are many alternative techniques available. These minimally invasive procedures offer the opportunity for a more conservative approach. Precise and accurate counseling facilitates better patient selection, based on the patient's desires, age and disease type, allowing treatment to be individually tailored to each woman.

Keywords: abnormal uterine bleeding • adenomyosis • endometrial hyperplasia • endometrial polyp • hysterectomy • hysteroscopy • myomectomy • PALM-COEIN • surgical treatment

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Abnormal uterine bleeding (AUB) is one of the most often encountered gynecological disorders in the general population and accounts for approximately 400,000 hospital admissions. It accounts for millions of office visits each year in the USA [1] and 5% of UK women aged 30–49 years visit a specialist every year for treatment of this disorder [2]. Approximately 10–35% of women report symptoms of AUB during their lifetime [3].

The impact of AUB is not only limited to population-based studies regarding incidence and prevalence, but it directly affects quality of life and entails high socioeconomic costs.

AUB is a huge entity, comprising different symptoms and different etiologies.

It is possible to differentiate between acute and chronic AUB disorders [4]. Chronic bleeding is characterized by abnormal volume, regularity and/or timing, with the vast majority of patients reporting symptoms in the preceding 6 months. Acute AUB typically requires immediate treatment [5,6].

Even though the aim of this paper is to emphasize the surgical possibilities we have for treating AUB, the authors recognize the important role of the medical therapies able to solve, when possible, in the least invasive way, symptoms and causes of AUB.

Surgery often plays an ambiguous role, although it may involve an invasive procedure and is sometimes considered as last resort, it is often more accepted as it provides a definitive treatment option. It is for precisely this reason we attempt to clarify the indication for surgical management of AUB.

Nowadays, due to increased maternal age and the delayed pregnancy desire, it may be more common to find women suffering from AUB and, at the same time, wishing to preserve their uterus and its functionality to be able to conceive. That is the reason why surgical treatment should be highly tailored to the patient and should be as less invasive as possible. Postoperative pain and symptom relief often are considered minor outcomes compared with fertility sparing even in cases

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treated, not so many years ago, with definitive surgical approach. So the treatment of AUB in fertile age women is strictly linked to their fertility preservation and their motherhood needs.

AUB is associated with multiple etiologies, the terminology of which is often confusing and lacks standard methodology for classification and management. In 2011 the International Federation of Gynecology and Obstetrics (FIGO) approved a new classification system, more commonly referred to as the PALM-COEIN (Figure 1) [4].

It stands for the major causes of uterine bleeding which are divided into nine categories: polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic and not yet classified. In the PALM group are those causes ascribed to organic/structural anomalies, consisting of disease entities more effectively treated surgically. The COEIN group, on the other hand, consists of disease entities not clearly defined by imaging or histopathology, in which surgery plays a more minor role, but is still considered a definitive choice in case of failed medical treatment.

This new classification system proposes to create a novel and practical system, for use by clinicians worldwide, particularly focusing on the surgical management of these disorders.

Following the PALM-COEIN scheme, we attempt to evaluate the optimum and most recent surgical techniques to treat AUB in fertile women.

As it is outside the scope of this review, we do not speak about the diagnostic procedures to evaluate an AUB. It is understood that ultrasound scans (included hysterosonography), MR and CT examinations, and direct vision hysteroscopy play a crucial role. In particular, we think that examinations based on ultrasound technology are the best approach for diagnosis, being cheaper than others, with high sensitivity and specificity. A good diagnosis is important not only for the patient and her consultant, but also for the surgeon, if needed.

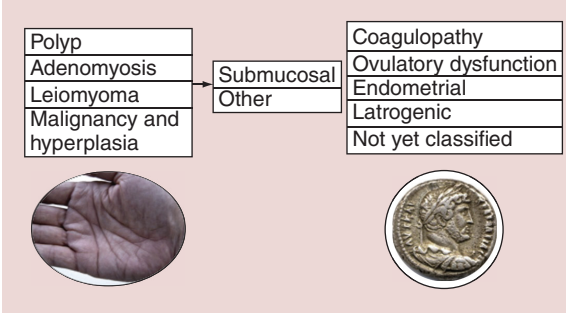

Figure 1. International Federation of Gynecology and Obstetrics PALM-COEIN abnormal uterine bleeding basic classification system.
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Polyps

The first 'P' of the classification system stands for 'Polyps.' It is a common gynecological disease and a frequent cause of AUB among fertile women. It is estimated that prevalence is around 7.8–34.9% (depending on the population, the diagnosis method and the definition of the polyp) [7–10]. In younger women (on whom this review focuses) the prevalence seems to be lower than in postmenopausal women (5.8 vs 11.8%) although there may be an element of bias due to improved and more frequent investigation for AUB diagnosis among postmenopausal women [8]. The real incidence is unclear due to a significant proportion of asymptomatic patients with endometrial polyps [11–14]. Women with endometrial polyps usually experience AUB in 68% of all cases, and 39% of premenopausal women with AUB have endometrial polyps [15].

The rationale for the treatment of this disease is essentially focused on relieving the symptoms of bleeding, while at the same time, obtaining a histopathological diagnosis to exclude rare malignant transformation estimated to occur in approximately 0–12.9% [10,16–21] of cases, with a higher predisposition for older women and those with significantly greater bleeding [22].

The different treatment options available include conservative medical management, conservative surgical or definitive surgical management. The choice of specific treatment is dependent on factors such as symptoms, pregnancy desire, risk of malignancy and operator skills.

Polyps with dimensions of around 1 cm can spontaneously regress (especially 10.7 mm polyps have a 27% chance of spontaneous regression in 12 months [14]), so, in these cases, it could be considered an expectant approach.

In any case polypectomy appears to be a good answer to AUB, with a respectable success rate. A review of the literature [23], including 10 studies, underlines as all procedures reported an improvement in symptoms of AUB (range 75–100%) at follow-up intervals of between 2 and 52 months. In particular, in the two studies restricted to premenopausal women, an improvement in symptomatology between 88 and 100% was demonstrated [24,25].

For many years the most commonly used technique was blind dilatation and curettage (D&C) and although it is no longer recommended, it still remains popular; a survey [26] from the UK in 2002 reported that 2% of gynecologists used blind dilation and curettage for the management of endometrial polyps, and 51% performed blind curettage after hysteroscopy for the removal of polyps. This could be due to a difficulty in changing habits in the oldest surgeons or in those who learn by them. Many studies have highlighted the

inefficiency of D&C (4% of complete removal) not only in the management of AUB (without imaging or hysteroscopic diagnosis), but also when performed following hysteroscopy, with a global success rate of lower than 50% of procedures and a high complication rate [27–31]. The use of ultrasound guidance is equally of limited interest [32].

The gold standard, therefore, for diagnosis and treatment is based on hysteroscopic techniques that allow not only a direct visualization, but also, in some cases, immediate removal. This kind of hysteroscopy in an outpatient setting, despite being a more common procedure, is performed in fewer instances than the classical approach in an operating room requiring anesthesia and hospitalization.

Hysteroscopic polypectomy is now considered a safe and effective method of treatment, in part due to its relatively low costs and quick return to normal life following surgery [33–35].

In any case it is not a risk free procedure and the patient should be well counseled accordingly.

Narrower sized hysteroscopes now provide a greater opportunity to avoid hospitalization and general anesthesia. A large-scale class II study reported 4863 consecutive operative outpatient hysteroscopies including 2306 for endometrial polyps, in which most small endometrial polyps were removed with minimal discomfort [36]. Not only after the first diagnosis by hysteroscopic visualization, but also contextually, setting up the so-called 'see-and-treat' hysteroscopy. A recent work by Gambadauro *et al.* outlines a see-and-treat polypectomy as a good technique, when performed with a 5-French instrument, but it should consider patient's pain, age and polyps dimension [37]. In selected cases, within an outpatient setting, the use of anesthesia such as paracervical block or intrauterine anesthetics may be considered advantageous [38].

For large diameter polyps cervical dilatation may be necessary requiring classical hysteroscopic resection with general or local anesthesia and wider diameter instruments.

The choice of instrument used and setting depends on surgeon's experience, availability, costs, location and size of the polyp. Electrosurgical loops (resectoscopic) are effective for removing large and sessile polyps with no recurrence, but with longer operating time and higher complication rates, whereas small forceps or scissors could be used when removing small polyps with an operating hysteroscope; however, a 15% recurrence rate has been reported [33].

Bipolar Versapoint (Gynecare, NJ, USA) system, is an example of an additional available technique. It minimizes cervical dilation compared with the operating hysteroscope and the use of saline solution rather than glycine, with a decreased risk of hyponatremia and its sequelae [14,39]. Another example is the hysteroscopic morcellator that removes polyp chips as it resects, allowing continuous vision, short operating time and less movement of instruments through the cervix with a decreased potential for cervical laceration and fluid loss [40,41]. The availability of these techniques may be limited, due to their spread and costs, but there are no randomized control trials to prove greater effectiveness with regard to improve clinical outcomes.

All these procedures are uterus sparing and they should preserve fertility. Sometimes a more aggressive surgical technique may be necessary, such as endometrial ablation or resection, which cannot guarantee further pregnancies. To allow these, it is also important to avoid uterine synechia. Intrauterine adhesions usually are caused by D&C, a technique less and less used. However, to our knowledge, there is not any strong evidence for any therapy on preventing them, even if data show good results for estrogen therapy, hyaluronic acid, intrauterine devices or amnion graft. As this article is focused on surgery, and not evidence for preventing adhesions, we will not discuss this any further.

Adenomyosis

First described in 1860 by German pathologist Carl von Rokitansky, adenomyosis is a benign gynecological disease of the uterus characterized by myometrial invasion by endometrial glands and stroma with deep abnormal growth in the muscle wall [42–45]. Adenomyosis could be classified into two forms: diffuse and localized. When the endometrial tissue in the myometrial thickness is well circumscribed it forms a nodule called adenomyoma, mostly made up of smooth muscle cells, where it is often easy to recognize a wall of the lesion and a cleavage plane [46].

Common symptoms of adenomyosis are dysmenorrhea (30%), menorrhagia (50%), abnormal bleeding (20%) and coexisting pelvic pain (80%) [43,47–48]. A presumptive diagnosis based on these symptoms is accurate in 25% of cases, even if 30–35% of patient with the disease are asymptomatic [49,50]. Even if imaging (transvaginal ultrasounds and MRI) can improve accuracy, diagnosis is based on histologic analysis alone. The supposed incidence varies greatly between 5 and 70% [47,51–52] and following hysterectomies it has been found in 20–30% of cases [52–54].

Even if hysterectomy is still the gold standard in the treatment of adenomyosis, it has become necessary to consider conservative approaches both to maintain fertility and for women wishing to preserve their uterus.

No medical treatment allows, at the same time, therapy and possibility of conceiving, being all based

on hormonal administration (continuous use of oral contraceptive pills, high-dose progestins, the levonorgestrel-releasing intrauterine device (LNG-IUD), danazol and GnRH agonists), with consequent ovulation suppression.

As a result, surgery plays a significant role, even in a conservative scenario.

A possibility for localized adenomyosis (adenomyoma) is removing the lesion considering it is similar if not the same as a leiomyoma, even if in case of focal adenomyosis is more difficult to expose the lesion, recognize clear margins and define the exact extent of disease. For these reasons it could be possible that residual adenomyosis is left behind with subsequent lower effectiveness with regards to symptomatology or relapse. Wood [55] evaluated this kind of surgery and he has found an efficacy of 50%. More recent studies seem to confirm suboptimal results in term of symptoms relief (dysmenorrhea remained in 41% of patients and 35% reported no reduction in heavy bleeding) [56], but, seem to show a good trend in terms of recurrence rate (1% vs previous study reporting up to 69% of relapse) [57], and in terms of pregnancy rate after surgery (61.5%) [58]. All these studies differ from patient selection, surgical approach and technique, years of follow-up and pathologist expertise, so it is difficult to make accurate overall evaluations. A separate consideration includes cystic variant of adenomyosis, typically afflicting young women: the juvenile cystic adenomyoma, first described by Tamura *et al.* [59]. Takeuchi in 2010 described a series of nine laparoscopic resection of juvenile cystic adenomyoma with significant improvement of associated dysmenorrhea and increased fertility [60].

Other conservative surgical approaches for adenomyosis include endometrial ablation and resection, myometrial electrocoagulation or reduction and uterine artery embolization.

Endometrial ablation or resection is surgical approaches used for adenomyosis in women wishing to preserve their uterus. These techniques are oppressed by high risk of failure, because it is not possible to go too deep on the myometrial wall, and there is a high risk of repeat surgery [61].

Similar to adenomyomectomy, is the endometrial reduction, that is performed by uterine incision and wedge resection removing a large part of myometrium, both laparoscopically and laparotomically. Literature shows limited number of cases, but it seems to emerge that the 'H' shape variant of the incision can give better results in term of pregnancy rates [62] and the removal as much of the adenomyotic lesion as possible, leaving up to 0.5 cm only of myometrium layer on both sides (Figure 2), seems having good outcomes [56].

Other procedures are the MR-guided focused ultrasound surgery (MRgFUS) and ultrasound-guided FU (USgFUS) [63]. A recent study confirmed good safety and feasibility of USgFUS with good results for both dysmenorrhea and menorrhagia (with significant reduction of bleeding at every follow-up from 1 month to 18 months after procedure, $p < 0.001$) [64].

Another procedure not recommended in women who wish to conceive is myometrial electrocoagulation due to the risk of uterine rupture for scar tissue replacing adenomyosis foci [65]. Performed laparoscopically, even if less invasive than classical surgical myometrial reduction or adenomyomectomy, it is less accurate in

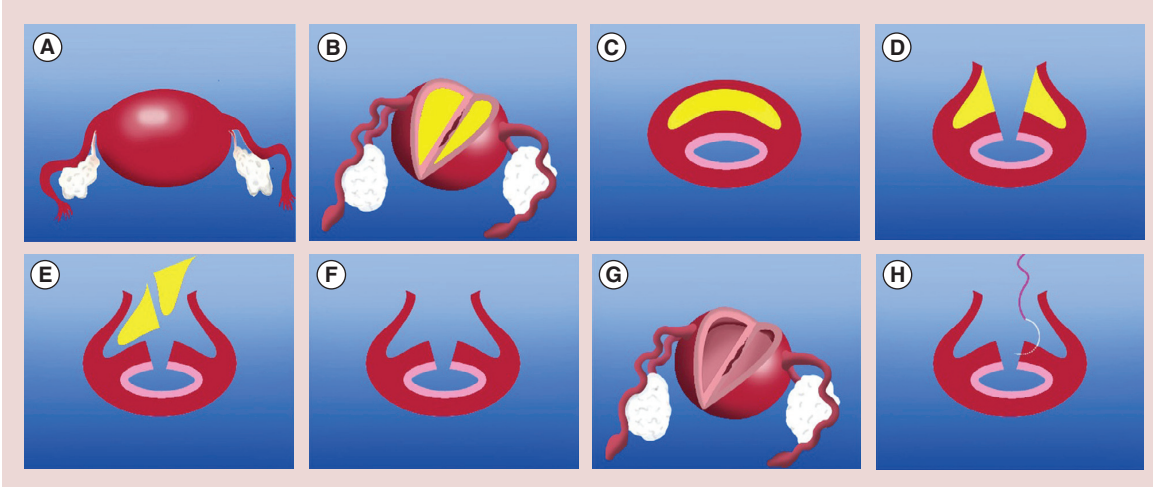

Figure 2. Adenomyomectomy procedure. (A–H) The adenomyomectomy procedure (yellow areas are the adenomyoma tissues). Starting from a saggital incision they perform adenomyomectomy and suture the uterus without entering the endometrial cavity.
For color images please see online at www.futuremedicine.com/doi/full/10.2217/WHE.15.12
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removing the lesions as it cannot be complete. There is a paucity of numbers of procedures in studies, but it has better outcome especially when associated with other techniques (endometrial ablation or resection and medical therapy) with improvement of the symptoms from 55 to 70% [55,65–67].

The last described procedure is uterine artery embolization (UAE), typically used for the treatment of leiomyomas. Its role in adenomyosis treatment is controversial due to frequent concomitant presence of myomas that reduce effectiveness of the procedure. When it is applied for adenomyosis alone, some studies show good outcomes. After 4.9 years 57% (of 54) of patients who underwent UAE reported reduction of bleeding; however, 19 of them (35%) relapsed [68].

Surgery for the management of adenomyosis includes many different alternative procedures and techniques. It can often be difficult for both the patient and the gynecologist to determine the best course of treatment. As result evidence-based practice should be adopted by gynecologists while also drawing on their own skills and experience to optimize patient care.

Leiomyomatosis

The most common female genital tract benign tumors are uterine myomas. It is estimated that 20–30% of reproductive aged women are affected by this disease [69] and it increases to 70% in 49-year-old women [70].

Symptoms are present in about 30% of patients and they manifest as AUB, subfertility, recurrent miscarriage and urinary frequency [71].

Traditionally the management of this disease is based on surgery (hysterectomy and myomectomy), although medical options are considered useful and effective as both progesterone and estrogen receptors can be present in myomas [72].

In 1999 leiomyomatosis was the surgical indication for 33% of hysterectomies performed in the USA, but nowadays in the last two decades this trend is changing, with an increase in more conservative approaches. Particularly myomectomy is the only surgical technique that allows fertility sparing, even if is still not very clear the effectiveness of the procedure in improving fertility and pregnancy outcome [73,74]. Most women ask to preserve uterus since they have not completed childbearing, which occurs in older age than before for social and economic reasons and thanks to oocyte donation as well. Not only women wishing pregnancy ask to maintain uterus, but they could ask it for personal reasons as well (worried for their sexual life and their femininity [75]).

Usually the indications for myomectomy are serious medical condition due to heavy bleeding with severe anemia and ureteral obstruction. In some cases myomectomy is requested also for AUB only, or a poorer quality of life for incontinence, urinary frequency, pelvic pain or pressure.

Uterine leiomyomatosis represents the L in the PALM-COEIN system, and this entity is subdivided into SM (submucousal) or O (other) and SM, itself, has a subclassification originally proposed by Wamsteker *et al.* [76] on the basis of endometrial cavity distortion (Figure 3).

The other myomas (IM and SS [intramural and subserosal, respectively] ones), especially when endometrial cavity is of a normal size, should not cause a lot of symptoms and their removal seems to be not effective on fertility improvement.

Actually the only submucousal myomas are involved in AUB and subfertility with higher likelihood, even if a 2012 Cochrane meta-analysis of literature showed no evidence for myomectomy (even of submucousal ones) in improving fertility [77].

An important message to give to the patient is the very low likelihood of a malign degeneration of the myomas. Leiomyosarcomas have low incidence (0.23%) and usually are a *de novo* transformation and are more frequent in postmenopausal age [78]. Given this benign natural history of myomas it could be possible to make the subsequent considerations about their management, even an attendant or medical one.

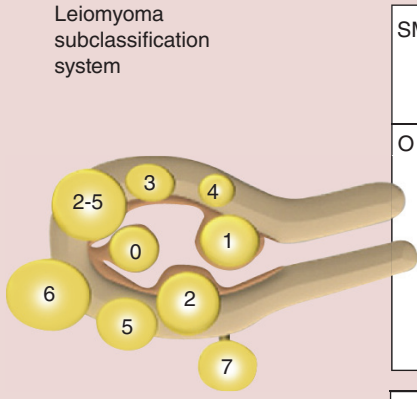
Hysteroscopic myomectomy is the least invasive approach currently available to treat submucousal myomas with good results [79–81]. The size of the myomas is the first limiting factor for a single myomectomy procedure, while intramural extension seems to be more difficult with a greater risk of complications [82,83].

Usually a myoma bigger than 5–6 cm is considered not eligible for hysteroscopic myomectomy. A recent study [84] confirmed this limit, suggesting that till 5 cm of diameter of submucousal myoma, hysteroscopic resection should be the first choice in case of AUB.

Indeed AUB symptoms find good relief by this kind of procedure and most of the studies show an effectiveness from 70 to 99% [85], but long term follow-ups show an increase of recurrences (probably due to incomplete removal and other functional bleedings) and the need of a second surgery.

A particularly hostile localization of SM is the lower uterine segment with extension to the cervix. These lesions could find an alternative option in the vaginal myomectomy described in a report published by Goldrath [86].

The management concerning intramural and subserosal myomas is essentially based on laparoscopic or abdominal myomectomy (LM and AM), but often this kind of lesions are not cause of AUB.



SM – submucosal	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
O – other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (specify e.g., cervical, parasitic)

Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively

Figure 3. International Federation of Gynecology and Obstetrics classification of myomas.
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Many studies tried to point out a definitive approach, but till now it seems an open issue. Probably the best way to give a right counseling to the patients is to propose the best alternatives by choosing a technique that could offer a good success, with the minor risk and pain, and what surgeons have available and are able to do. In terms of AUB control neither laparoscopic myomectomy nor abdominal (minilaparotomic one as well) has shown clear advantages in term of primary outcomes (fertility or control of bleeding), but it is well known that the minor invasivity of the laparoscopic approach even if some studies seem to suggest a better outcome for fertile patients that underwent to LM for symptomatic leiomyomas [87]. LM has demonstrated a minor operative blood loss, less haemoglobin loss, more rapid hospital discharge, reduced postoperative pain and less overall complications (with a similar incidence of major complications and recurrence rate) [88,89]. Recently the procedure has been put under strict control due to the US FDA's statement [90] due to the risk of diffusion of leiomyosarcoma related to the use of 'power' or electromechanical morcellation during laparoscopical myomectomies (and laparoscopical supracervical hysterectomy [LSH]), but we think that, if the patient is well evaluated and the surgeon has high skill in the procedure, advantages of this approach could still be greater than this low risk or, if possible, the transvaginal extraction of the myoma is a quick and safe alternative [91].

Another technique that has not been well studied is vaginal myomectomy. A recent literature review showed good results, comparable with those from LM or AM. It is difficult to assess the exact role of the vaginal approach, due to the lack of data, but many authors suggest to confine it for myomas not bigger than 8 cm and localized only on the posterior uterine wall [92].

Directly related to the AUB symptomatology and the choice of the surgical ways the literature tried to investigate the opportunity of a preoperative GnRHa administration. A Cochrane meta-analysis [93] and a more recent review [94] stated that GnRHa pretreatment does not advantage in terms of operative times in LM, despite myoma shrinkage, due to the greater difficulty to recognize the cleavage plane. However the same review demonstrated a further reduction of intraoperative bleeding and increased postoperative hemoglobin concentration in patients undergoing LM. Another preoperative drug administration recently proposed prior to myomectomy is a daily regimen of selective progesterone-receptor modulators. Two studies compared ulipristal acetate (UPA) with placebo [95] and with leuprolide [96] acetate (GnRHa) for the treatment of symptomatic uterine fibroids before surgery. Both studies showed good results on controlling bleeding, reducing size of fibroids and with low rate of hot flashes (in comparison with GnRHa administration). Further studies are needed to evaluate the role of UPA before surgery, or to delay it or even to avoid it. Since UPA showed good results, it could be possible, as

already suggested [97], that fibroids management could change in the next few years and more data are needed to asses the role of UPA to avoid recurrences.

The new entrance of robotic assisted laparoscopies till now has not demonstrated benefits in comparison with LM and its use appears to be not justifiable [98] , even if the hypothesis was a better uterine suture and a lower risk of scar rupture during pregnancy (1% risk of uterine rupture in pregnancy after LM [99]). That is the reason why many surgeons propose caesarean section for pregnancies after myomectomy (both LM or AM).

The real incidence of uterine rupture after laparoscopic myomectomy seems to be not necessarily greater than the abdominal one, but needs more data to be evaluated. Two recent reviews [100,101] of literature suggest no increased risk of uterine rupture after laparoscopic myomectomy and, even if evidences are poor due to the low rate of incidence, many authors suggest to limit electrosurgery coagulation during the procedure to reduce that risk and to do a multiple layer uterine closure.

Likely for adenomyosis, also leiomyomatosis could find benefits by alternative approaches to traditional surgery. One of the most investigated is the UAE. In 2012 the Cochrane Library [102] published a meta-analysis on this issue and it confirmed a good patient satisfaction and less hospital stay and quicker return to normal life in comparison of any type of surgery. On the other side, UAE seems to have a higher risk of minor complications and higher rate of further surgery within 2–5 years from the first procedure and, since it may be associated with a higher risk of preterm labor, intrauterine growth restriction and postpartum hemorrhage, it should be carefully suggested in patients with future pregnancy desire. Similar results come from localized uterine artery occlusion [103,104], both with electrodessication or clips managed laparoscopically and with coils deposited in the uterine artery [105].

Other procedures less common and not yet standardized include leiomyoma ablation or myolysis, hypothermic ablation, hyperthermic ablation by laser and radiofrequency electrical energy (Nd:YAG or RF) and ablation by focused ultrasound energy (HIFU). Myolisis appears to be a feasible alternative [106], but all these techniques need more study and analysis. RMg-FUS is the best investigated and its clinical results are promising [107] but it is needed a good patient selection and large scale clinical trials for a better comparison with the others techniques [108].

Even if the role of myomas in fertility is still unclear (especially for the IM and SS ones), surgery is often performed when there is no other evident cause of sterility, so it is important to develop not only a uterus-preserving technique, but also a fertility-improving approach. Always keeping in mind fertility desire and outcome after surgery, myomectomy seems to be the best choice, also compared with UAE [102] showing statistically significant ($p < 0.05$) differences on pregnancy rate of 50 versus 78%, delivery rate of 19 versus 48% and miscarriage rate of 53 versus 23%, after UAE and after myomectomy, respectively.

Malignancy

The last letter of the 'PALM' acronym stays for 'Malignancy,' meaning AUB caused by endometrial transformation toward cancer or precancer lesion. This entity is less common in reproductive age women than older ones, but it should always be considered, even if it was to rule it out.

Endometrial carcinoma (endometrioid type particularly) and its precursors are characterized by an hyper/relative estrogen ambient with consequent endometrial stimulation to proliferation of glandes and epithelial changes. So it explains the common symptom of AUB in these cases.

Sampling of endometrial tissue is an important approach in fertile age women with AUB. Although endometrial malignancy is found rarely among fertile age women with AUB, it must be excluded prior to any surgical intervention

One of the best goals of clinicians and pathologists is to recognize the lesion as soon as possible, with an early diagnosis of precancer lesions. These are usually grouped on the basis of Kurman's classification [109] and called 'atypical endometrial hyperplasia' (AEH) to which, recently, has been added a new quantitative classification [110] that calls the cancer precursor: 'endometrial intraepithelial neoplasia' (EIN). The first study is at the basis of the 1994 4-Class WHO schema [111] and it recognizes the well known four categories on the evaluation of nuclear atypia and glandular complexity: simple hyperplasia, complex hyperplasia, simple hyperplasia with atypia and complex hyperplasia with atypia, but they badly correlate with clinical management.

The other schema has been developed by the International Endometrial Collaborative Group. This one seems being a better outcome predictor, better interobserver reproduced [112]. Even if both the diagnosis of EIN [113] and atypical hyperplasia [114] have positive predictive value [115], the NIH recommends EIN as a better schema, appearing to be better tailored on distinguishing between premalignant lesions and which are not [116].

In case of suspecting AEH/EIN, surgery has the first role to make the diagnosis, by sampling the endometrial tissue. This is possible by both curettage and biopsy but both are not able to reach the goal of excluding any like-

lihood of cancer, due to their inability to make a wide and satisfactory enough sampling of the cavity [117]. This could be less important in those cases where hysterectomy has already previewed in the management, that can not be the routine in fertile women.

For women wishing to preserve uterus surgery has quite no place as endometrial ablation could not be acceptable, while medical treatment (local or systemic progestin administration) has a role if the patient is kept under strict surveillance [116].

Otherwise total hysterectomy (with or without bilateral salpingo-oophorectomy) is the gold standard in treatment of AEH/EIN being curative, effective and provides a definitive diagnosis. Supracervical hysterectomy (both laparotomic and laparoscopic) is not recommended [118].

Furthermore all the lesions discussed above (PAL) could have their malignant (or premalignant) equivalent. In these cases it is evident how important is the answer of the anatomopathologist to the tissue sample coming from the first surgery. As for AEH/EIN or endometrial cancer, also for the other malignant lesion total (or radical) hysterectomy is the only surgical approach.

COEIN

All the diseases causing AUB included in the second part of the PALM-COEIN system are usually not associated to organic or structural entities, so surgery could be less effective or, at least, not the first choice in the management.

Cases where medical treatment has failed and/or are not eligible for that could benefit of a surgical approach.

Endometrial ablation or resection is indicated for women wishing to preserve their uterus, but not wishing to bear children. There are several techniques such as global ablation, rollerball resection or yttrium aluminum garnet laser (Nd:YAG). As is intuitive, the deeper the lesions within the myometrial wall, the poorer the success of the rollerball resection, as demonstrated in two studies [55,119]. This is because it is not possible to resect deeper than 3 mm, as an arterial layer lies around 5 mm under the myometrial surface [55]. Also global endometrial ablation (both with thermal balloon and radiofrequency ablation) shows poor results with high risk of failure and repeat surgery (second ablation or hysterectomy) [61].

We think that, when it is not possible to preserve the uterus and/or where there is no pregnancy desire, hysterectomy is the best procedure, being definitive and curative. In particular, the laparoscopic approach allows a minimally invasive surgery, with low risk of complications and no risk of recurrence and no further surgery.

Hysterectomy

Hysterectomy represents the most common gynecological procedure in the world and a third of 60-year-old women underwent this surgery [120].

Its effectiveness in improving AUB symptoms, being curative and definitive, is well recognized.

Even if it is the most common gynecologic surgical procedure, it still has, as any kind of surgery, some complications, that lessen as surgeon experience increases. Those complications are: hemorrhage, infection, thromboembolism, injury to viscera and neuropathy. Their incidence ranges depending on the type of hysterectomy, surgeon's skill and study design.

Nowadays the debate is oriented on the comparison between it and the other less invasive procedures and, inside hysterectomies, between the different approaches available (open surgery, vaginal and laparoscopic and total [TLH] or supracervical ones).

Literature shows a lot of reviews and meta-analysis on that, but there is not a definitive answer, because clinical practice meets real patients and not only the theoretical ones and each one of them needs a personal counseling and the best fitted approach.

Hysterectomy is considered highly costly at the beginning, but has low cost later on, while other treatments have low primary costs, but they could be much more expensive in the long run if they had not resolved the problem. Unlikely there are few studies analyzing the cost–effectiveness of hysterectomies and those doing it are difficult to compare each other with no strong evidences [121].

A Cochrane Library publication tried, in 2009, to compare the different approaches of hysterectomies. In its conclusions the authors evidenced vaginal hysterectomy (VH) as the first choice, before laparoscopic hysterectomy (TLH) and, third, abdominal hysterectomy (AH), as there were no differences in term of outcomes, but just in recovery times and costs. At the end, they underlined the importance of the woman's choice, discussed with her surgeon [122]. Same conclusions reached Johnson in 2005, suggesting that, when VH is not possible, the second choice is LH even if, according to their analysis, it has greater risk of bladder and ureter injury [123]. Always on the same direction goes a recent meta-analysis that compares VH versus laparoscopically assisted vaginal hysterectomy. It shows no statistical differences in complications, conversion rate, hospital stay, blood loss, duration of paralytic ileus and weight of the surgically treated uterus and just a shorter operative time for VH [124].

Another Cochrane has compared with tal hysterectomies (TLH) versus subtotal ones (LSH; both laparotomic and laparoscopic), finding no differences between the two procedures [125]. On the other side, laparoscopically

assisted vaginal hysterectomy shows lower early postoperative pain scores and complication rates when compared with minilaparotomic hysterectomy [126].

An open issue remains the comparison between LSH, as the less invasive laparoscopical approach, and the two other mini-invasive procedures: TLH and VH. A recently published work evidences as LSH meets high patient's satisfaction and reduces cyclic pelvic pain [127].

Also when compared with the less-invasive options of endometrial ablation, levonorgestrel intrauterine system (LNG-IUS), and medications, no one can strongly assure to become the gold standard in AUB treatment, but everything is a tradeoff between effectiveness and risks [128].

Expert commentary

The modern trend in approaching AUB is related to the reduction of the global number of hysterectomies. A conservative surgical management of this common symptom is mandatory independently from the need of pregnancies. Conservative endoscopic surgery and medical treatment of AUB are now facilitated by the use of the PALM-COEIN classification. The knowledge of different causes (organic or not) of AUB consents a more flexible and tailored approach to the disease.

Conclusion

Surgical management of AUB is challenging both for women and physicians. New medical treatments are always flanked by new surgical and alternatives techniques. The best way to counsel the patient that is necessary to tailor the treatment is to listen to the woman, to her needs and her wishes and to offer an up-to-date view of the state of the art.

Future perspective

The number of surgical and medical strategies is increasing and it is not easy to choose among a big offer, both for the patient, and for the doctor. Many factors have to be considered and more awareness is due. Since pregnancy desire is being always more and more scheduled and planned, maternal age is growing and, with it, the importance of the best choice of a tailored therapy to treat AUB in fertile age. In the future all the minimally invasive procedures will replace the actual common definitive approach. New technologies as robotics or new targeted drug development will consent this evolution in treating abnormal uterine bleeding. This could minimize operative time and costs, and increasing patients satisfaction.

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Executive summary

- Abnormal uterine bleeding is the most common gynecological disease and its etiology is classified by the 2011's PALM-COEIN system.
- The best treatment for endometrial polyps is hysteroscopic resection and, where possible this can be performed in an outpatient setting. Dilatation and curettage should be avoided.
- The gold standard for the treatment of adenomyosis is hysterectomy, but local resection and removal have good results as new minimally invasive techniques, even if more clinical trails are necessary to further evaluate procedures and outcomes.
- Leiomyomatosis is symptomatic mostly due to submucousal myomas which could be removed by hysteroscopic resection if <5–6 cm diameter.
- Conservative surgery in the management of endometrial premalignant lesion is quite limited, as their treatment is medical or definitive (total hysterectomy).
- Hysterectomy is the definitive treatment of abnormal uterine bleeding and it should be performed by vaginal or laparoscopic route and, if possible, it should be considered laparoscopic supracervical one, being a minivasive and well perceived technique.

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• **Less-invasive treatment options for abnormal uterine bleeding result in improvement in quality of life but carry significant risk of retreatment caused by unsatisfactory results.**