

## MANAGEMENT OF ENDOMETRIAL MODIFICATIONS IN PERIMENOPAUSAL WOMEN

RENATA NICULA, NICOLAE COSTIN

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### *Abstract*

*Perimenopause has a variable length and time of onset and is characterized by its variability in hormonal levels. The histological changes in the perimenopausal endometrium may be represented by nonproliferative or proliferative benign or malignant lesions. A commonly encountered manifestation of endometrium lesions during menopausal transition is the abnormal uterine bleeding (AUB). The clinical management of AUB must follow a standardized classification system for optimal results. The medical and surgical treatment must be adapted according to age, risk factors, symptoms, and cycle irregularities. Use of alternative therapies and proper diet may result in improved long-term outcomes.*

**Keywords:** perimenopause, endometrium histopathology, clinical management.

### **Introduction**

Perimenopause (often referred to as the menopausal transition) is the time period during which women go from premenopause (the reproductive years) into menopause [1]. The median length of perimenopause has been estimated to be any time between 4 [2] and 11 years [3], which includes the year following the last cycle. Women are most likely to exhibit signs of perimenopause sometime in their 40s, although some women exhibit signs as early as their 30s or as late as their 50s [4]. There are epidemiological surveys which suggest [5] that approximately as many as 10% of women in their early 30s could be approaching their perimenopause transition.

### **Physiopathology**

The menopausal transition is an imprecise period and can be established from the moment of appearance of menstrual disturbances and elevation of the serum follicle-stimulating hormone (FSH) level, which is up to 12 months after the last menstrual period [6]. The perimenopause is characterized by its variability in hormonal levels [7] with increasing shortage of ovarian hormones and anovulation [8]. In the perimenopausal period an intermittent ovulation or even a chronic anovulation take place, therefore the

progesterone levels are low, because there is no corpus luteum. The ovaries are still producing oestrogen, which allows continued proliferation of the endometrium; the thickened endometrium outgrows its blood supply, undergoes focal necrosis and shedding begins. The shedding is not uniform, bleeding tends to be irregular, prolonged and heavy. The chronic endogenous oestrogen stimulation of the endometrium, unopposed by adequate progesterone levels can lead to endometrial hyperplasia and cancer [9].

Chronological age fairly well predicts ovarian response, upcoming perimenopausal and menopausal transition. The traditional staging methods provide only categorical determinations of reproductive age (pre-, peri-, postmenopause) on the basis of indicators (e.g. hormones) that can be unreliable or unchanged until the function of the ovary is severely compromised. Some findings in perimenopausal women suggest the existence of a pituitary insensitivity to estrogens [10]. A substantial rise in FSH levels occurs relatively late when the perimenopausal transition is already present [11]. In the early stage of the menopausal transition, estradiol levels remain normal or are even elevated (by increased aromatase activity), the levels of progesterone are decreased and occasional spontaneous ovulations may occur. In the late stage of the menopausal transition, the menstrual irregularity and the fluctuation of serum FSH, inhibin B and estradiol levels increase and the determination of the anti-Mullerian hormone level

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is more accurate during this period [6]. There are studies which have shown that anti-Müllerian hormone (AMH) is a predictor for the occurrence of perimenopausal transition (cycle length irregularity) within 3–5 years [12,13] at levels <0.92 ng/ml. AMH is suitable as a screening test and may replace FSH which gains relevance only in the late reproductive phase [14]. Also, the antral follicle count (AFC) is a more accurate, well-validated marker reflecting reproductive aging [15].

### **Etiopathogenesis and histopathology**

The histological changes in the perimenopausal endometrium can be classified as nonproliferative lesions (atrophic, inactive, secretory, endometritis, endometrial metaplasia) or proliferative lesions: benign, noninvasive (endometrial polyps, endometrial and stromal hyperplasia) or malignant, invasive (endometrial cancer) [16,17]. The incidence of endometrial hyperplasia and endometrial carcinoma are more common in the perimenopausal and postmenopausal women [18]. The risk of endometrial hyperplasia may exceed 30% in perimenopausal women with abnormal uterine bleeding [19,20,21]. Perimenopausal women had significantly more straight arterioles than women prior to perimenopause at the late secretory stage, with significant increases in  $\alpha$ -actin staining in showing perimenopausal symptoms [22]. A less frequently encountered pathological diagnosis is endometritis (between 6.4 and 20.7% cases) [23,24]. Multiple micro-polyps (1 mm or less in size) are positively diagnostic of endometritis; coupled with clinical symptoms, stromal edema and local hyperemia micro-polyps make a case of chronic endometritis [25]. Endometritis as a cause of AUB should be kept in mind and evaluation and medical therapy can obviate a more aggressive therapy in such cases [25]. The secretory phase is the least seen, only in about 10% or less of cases [20].

The causes of abnormal uterine bleeding (AUB) in non-gravid women of reproductive age are standardized in the FIGO classification system (PALM-COEIN) [26]. PALM group includes five entities with structural etiologies of AUB that can be diagnosed with imaging techniques and/or histopathology (polyp; adenomyosis; leiomyoma; malignancy, and hyperplasia). COEIN group includes non-structural entities that are not diagnosed by imaging or histopathology: coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified [27]. According to FIGO classification, women with no structural cause for AUB, should actually be differentiated into one or a combination of the following three etiologies: coagulopathy (AUB-C), disorder of ovulation (AUB-O), or primary endometrial disorder (AUB-E) [26].

In a study of endometrial pathology in abnormal uterine bleeding it has been found that the commonest pathology causing abnormal uterine bleeding (AUB) is disordered proliferative pattern (20.5%); other causes

include benign endometrial polyp (11.2%), endometrial hyperplasia (6.1%), carcinoma (4.4%) and chronic endometritis (4.2%) [28].

Uterine leiomyomas or fibroids are benign smooth-muscle tumors of clonal origin [29]; they have an incidence which increases with age from menarche to perimenopause [30]. Regardless of their generally benign neoplastic character, uterine fibroids are responsible for significant morbidity in a large proportion of women of reproductive age [31].

### **Symptomatology of perimenopause**

#### *Physical symptoms*

During the menopause transition, the vasomotor symptoms (VMS) (hot flashes, night sweats) are experienced by most women [32,33,34]. The more disturbing symptoms of premenstrual syndrome (physical symptoms - breast tenderness, abdominal bloating, nausea, headache, and emotional symptoms) [35] can increase in severity and duration [16]. The hormonal instability during the perimenopausal period also increases migraine incidence [36]; preexisting migraine can remain unchanged, improve, but may also worsen during perimenopause [37].

Perimenopausal women can experience rapid bone loss [38] and increased risk of cardiovascular diseases (CVD) [39,40]. Also, in perimenopausal women there is an association between VMS and metabolic health outcomes (type 2 diabetes and insulin resistance) [41]. It is important to be noted that the occurrence of low to severe problems during perimenopause is positively associated with overweight/obesity [42], but the body lean mass, not fat mass, is a significant contributor to femoral bone mineral density in perimenopausal women [43].

The prevalence of vaginal dryness increases with the menopausal stage; in early perimenopause, the prevalence can be 4% [44,45]. The symptoms result directly from the decline in estrogen. Coexisting urinary problems, such as frequency, urgency, nocturia, dysuria, and recurrent urinary tract infections, can be often associated with vulvovaginal atrophy [46].

#### *Menorrhagia and fibroids*

Up to 14% of women experience irregular or excessively heavy menstrual bleeding [47]. Clinically, the gynecologists categorized the patient's bleeding pattern, before using the FIGO classification, into 1 of 4 types: irregular bleeding, heavy but regular bleeding (menorrhagia), severe acute bleeding, and abnormal bleeding [48]. Menorrhagia is heavy menstrual bleeding and is classically defined as a loss of >80 ml/cycle [49,50]. Menorrhagia affects  $\geq 9\%$  of all women, increasing to 20% during the perimenopause [22]. Heavy menstrual bleeding (HMB) is an important cause for anemia in perimenopausal women; generally, HMB is a symptom of ovulatory disorders, primary endometrial disorders, fibroid, adenomyosis, endometriosis or genital malignancies

[26,51]. The anovulatory bleeding, which is more common near menarche and the perimenopause, is often irregular, heavy, and prolonged; it is more likely to be associated with endometrial hyperplasia and cancer [52].

The variable symptomatology of fibroids often begins as an insidious feeling of pelvic discomfort; the clinical symptoms may include pelvic pressure and pain, congestion, heaviness, bloating, urinary frequency, constipation, dyspareunia, reproductive dysfunction and abnormal vaginal bleeding [31].

#### *Depression and psychological stress*

Various psychological symptoms diminish the overall women's quality of life [53]: anxiety, irritability [33], poor concentration, depression [35], mood swings, and other changes that may impair personal or social interactions [34,54]. During perimenopause there is a positive, bidirectional association between VMS and depressive symptoms [55]. Perimenopausal depression is increasingly recognized as a new subtype of depression with specific clinical characteristics [56]. Sleep disturbance is an important change in menopause because it affects the quality of life and may lead to depression [57]. A greater psychological stress may accelerate reproductive aging and the antral follicle count decline across women [15].

### **Investigations and diagnosis strategy**

#### ***Blood and other tests***

For the first step a gravid context must be excluded by patient history and urine/serum assay could be performed for the presence of the b-subunit of human chorionic gonadotropin [26,52].

A full blood count should be taken. A thyroid function test should only be performed if there are indicators for thyroid disorder. Testing for coagulation diseases such as von Willebrand disease is recommended for those with indications. Hormone testing of women who have heavy menstrual bleeding is not recommended [58].

After the exclusion of gravid status, the strategy sequence for the diagnosis of causes of non-structural abnormal uterine bleeding may be as follows: confirming the uterine origin and chronic pattern → investigating for structural cause (PALM group) → structural cause excluded: consider non-structural etiology (COEIN Group) → determining ovulatory status (AUB-O) or exclude iatrogenic cause (AUB-I) or screening for coagulation disorders (AUB-C) → if no identified causes, then consider AUB-E [27].

#### ***Ultrasound***

If imaging is indicated, transvaginal ultrasound should be the first line imaging method for abnormal uterine bleeding [52]. Transvaginal ultrasound (TVS) is a cost-minimizing screening tool for perimenopausal and post-menopausal women with vaginal bleeding [59].

The interpretation of endometrial thickness in the

perimenopausal woman is dependent on the time of the menstrual cycle during which the ultrasound is performed. Most accurate results are achieved if performed on days 4–7 of cycle, when menses have ceased [58]. An endometrial thickness less than 6 mm is usually considered as non-hyperplastic [60]. Even an endometrial thickness of  $\leq 5$  mm in a symptomatic postmenopausal woman is associated with a low endometrial cancer risk (1% chance) [61,62]; unfortunately, there is no consensus on what normal endometrial thickness is in premenopausal patients or in patients taking hormone therapy [63].

TVS is used to identify parietal abnormalities, such as fibroids and adenomyosis, and to screen for thickened endometrium [25]. It can detect uterine tumors, polyps, endometrial and myometrial abnormalities and can assess ovaries, but it is less sensitive and specific than saline infusion sonohysterography [47]. There are cases in which TVS cannot distinguish endometrial hyperplasia from benign polyps because both conditions can cause thickening of the endometrium, are hyperechoic and can contain cystic spaces [64]. TVS can reach 60 to 92% sensitivity and 62 to 93% specificity for diagnosing intracavitary abnormality in premenopausal women [65,66]. Occasionally (in 5% to 10% of cases), a woman's endometrium cannot be identified on ultrasound, and these women need further evaluation [67].

#### ***Sonoelastography***

Today, a new non-invasive method of examination, sonoelastography (SEG), which is based on the ultrasonic examination of tissues softness, is constantly developing. However, there is still a lack of evidence regarding endometrial assessment using SEG [67]. Thus, Preis et al. [68] in a group of 35 perimenopausal patients obtained a sensitivity value of sonoelastography for endometrium hyperplasia as high as 100%.

#### ***Sonohysterography***

Saline infusion sonohysterography involves the introduction of 5 to 15 ml of saline into the uterine cavity during transvaginal sonography [52]. Saline infusion sonohysterography may be used to evaluate menorrhagia [47]. It has the utility of transvaginal ultrasonography with improved capacity to diagnose endometrial abnormalities [65,66], but is more expensive than transvaginal ultrasonography and has limited availability compared with transvaginal ultrasonography [47].

The ultrasound may include a saline-infused sonohysterogram, especially when the endometrial stripe is thick, because of the increased sensitivity for endometrial polyps and submucous fibroids [69,70]. This method presents greater discrimination, up to 88 to 99% sensitivity and 72 to 95% specificity for detecting the location and relationship to the uterine cavity of the intracavitary abnormality in premenopausal women [65,66]. As a result,

it can also obviate the need for MRI in the diagnosis and management of uterine anomalies [52].

### **Endometrial Biopsy**

Histologic evaluation of the endometrium should be done in all patients in whom endometrial cancer is suspected [61]. An endometrial biopsy (with or without hysteroscopy) is indicated if the perimenopausal women has an endometrial thickness over 5 mm [58]. If no etiology is found on ultrasonography, for women 35 years or older with recurrent anovulation, women with risk factors for endometrial cancer, and women with excessive bleeding unresponsive to medical therapy should undergo endometrial biopsy [47,71] or direct visualization of the endometrium with hysteroscopy [72].

The endometrial biopsy is readily available and has a low complication rate [73]. It has contraindications in active pelvic inflammatory disease, clotting disorders or cervical infection or pathology [73]. The endometrial biopsy is 91% sensitive and 98% specific for detecting cancer and 82.3% sensitive and 98% specific for detecting hyperplasia with atypia [74].

### **Diagnostic hysteroscopy**

Diagnostic hysteroscopy is a highly specific, accurate, safe and clinically useful tool for detecting intrauterine abnormalities and to direct the treatment toward the specific pathology [58]. It allows direct visualization of the uterine cavity and allows for directed biopsy at time of procedure [47]. In order to achieve optimal visualization, diagnostic hysteroscopy should be performed in the follicular phase of the cycle, and if the ultrasound examination is inconclusive or suggests intrauterine pathology [58].

Hysteroscopic examination should be considered in patients with persistent uterine bleeding with benign endometrial sampling or insufficient sampling [61]. Hysteroscopy is more sensitive for the detection of polyp and other benign endometrial lesions than D&C or endometrial biopsy [75]. The diagnostic hysteroscopy is more expensive than transvaginal ultrasonography [65] and does not evaluate the myometrium or ovaries. In pre- and postmenopausal women it presents 94% sensitivity and 89% percent specificity for detecting intracavitary abnormality [72].

### **Dilation and curettage**

Dilation and curettage used to be a very common procedure performed for women with menorrhagia [9]. However, it is ineffective in reducing menstrual blood loss in the long term [76] and is only useful when combined with hysteroscopy for evaluation of the intrauterine cavity. The uterine curettage for endometrial biopsy to rule out endometrial causes of AUB should be reserved for perimenopausal women [19]; therefore endometrial curettage plays an important role in the timely diagnosis of

preneoplasia and malignancy [21].

Even though dilatation and curettage is unacceptable as a screening test [77], it remains the diagnostic method of choice for the evaluation of the endometrium in the following situations: non-diagnostic office biopsy in a high-risk patient when underlying endometrial cancer is suspected; benign endometrial biopsy and persistent bleeding; insufficient material on the endometrial biopsy with a thickened endometrial lining on ultrasound examination; office endometrial biopsy is impossible because of the patient's discomfort and/or anxiety or significant cervical stenosis [61].

### **Screening programs**

Due to the fact that the breast is a hormone-dependent organ that responds to the hormonal changes of perimenopause, breast cancer screening should target women of 50–75 years of age and also be discussed with women from age 40. The absolute benefit of detection increases with age, whereas the false positive rate decreases with age [6].

The incidence of cervical cancer has two peaks, with the first being between five and ten years after the first sexual intercourse and the second beginning at the age of 40. The co-test, which associates the cytology with a test for HPV types, has been shown to be superior to cytology alone in the identification of preinvasive lesions [6].

Colorectal cancer screening reduces disease mortality and should begin at the age of 50 for women who are at average risk for colorectal cancer [6].

### **Management and treatment**

#### **Medical treatment**

Once malignancy and significant pelvic pathology have been ruled out, medical treatment is an effective first-line therapeutic option for abnormal uterine bleeding [52]. Even if there is a significant spontaneous rate of resolution of heavy menstrual bleeding in naturally menstruating women during the perimenopausal years [78], the medical treatment is the first-line therapy in AUB in order to decrease blood loss [27,52]. The American College of Obstetricians and Gynecologists stated that as "AUB-O is an endocrinologic abnormality; the underlying disorder should be treated medically rather than surgically" [79]. Women with AUB-C are best managed in a multidisciplinary approach including gynecologist and hematologist [27]. In AUB-E situation the use of both hormonal and non-hormonal therapy is recommended [27,52]. Women's treatment preferences are linked to the stage of their reproductive life and severity of their symptoms and are also affected by their level of education and employment status [80].

Systematic reviews show that non-steroidal anti-inflammatory drugs (NSAIDs), tranexamic acid (synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect), danazol (derivative of the synthetic

steroid ethisterone) and intrauterine progestogens are all effective in reducing the amount of blood lost per cycle [81,82,83,84].

#### *Nonhormonal Drugs*

The non-hormonal options, such as non-steroidal anti-inflammatory drugs and antifibrinolytics can be used effectively to treat heavy menstrual bleeding that is mainly cyclic or predictable in timing [52].

Tranexamic acid (Lysteda), is more specific for the treatment of ovulatory bleeding, but is considerably more expensive than other available therapies [47]. Two 650-mg tablets taken three times a day for the first five days of the cycle decreased bleeding significantly more than NSAIDs [82]. Must be used with caution in patients with history or risk of thromboembolic or renal disease and is contraindicated if the patient has active intravascular clotting or subarachnoid hemorrhage [47].

NSAIDs decrease prostaglandin levels, reducing menstrual bleeding [81]. Non-hormonal options such as non-steroidal anti-inflammatory drugs and antifibrinolytics can be used effectively to treat heavy menstrual bleeding that is mainly cyclic or predictable in timing [52]. Ibuprofen can be used for treating dysmenorrhea in dosage of 600 to 1,200 mg per day, five days per month, beginning first day of menses and continuing for five days or until menses ceases. Naproxen sodium can be used in dosage of 550 to 1,100 mg per day, five days per month, but with caution in patients with gastrointestinal risks. Mefenamic acid can be used in dosage of 1,500 mg per day, five days per month [47,81,85]. In one small study, naproxen sodium (Anaprox) and mefenamic acid (Ponstel) decreased flow volume by 46 and 47 percent, respectively [85]. There is no evidence that a certain NSAID is more effective than another [81], but cost varies considerably.

#### *Hormonal therapy*

Histological findings of hyperplasia without atypia may be treated with cyclic or continuous progestin [47]. In case of severe acute uterine bleeding in the nonpregnant patient high-dose estrogen (orally or intravenously depending on bleeding severity) can be used and then a tapering schedule of oral contraceptives [48]. The use of hormonal contraceptives in healthy women over 40 without menstrual disorders may reduce gynaecological cancers, bone mass loss, and can prevent the ovarian function cessation, other possible beneficial effects in depression and cardiovascular disease [86]. Also, traditional and novel forms of hormonal therapy, including Tibolone (synthetic steroid medicine used for hormone replacement therapy) and selective estrogen receptor modulators like tamoxifen and raloxifene should be further investigated for the treatment of depression in perimenopausal women [56].

There are also some studies which observed that women taking combined oral contraceptive pill (COC), containing an oestrogen and a progestogen, have reduced menstrual blood loss [87,88]. In case of anovulatory

bleeding COC may be used [71] in dose of  $\leq 35$  mcg of ethinylestradiol monophasic or triphasic pills. But the COC are not being suitable for all perimenopausal women as the risks outweigh the benefits in smokers over the age of 35, in women with risk factors for cardiovascular disease such as obesity and hypertension [89], in case of personal history or high risk of deep venous thrombosis or pulmonary embolism, multiple risk factors for arterial cardiovascular disease, history of breast cancer, and severe cirrhosis or liver cancer [90], although it does protect against endometrial and ovarian cancer [89].

Oral administration of progestogens decreases cyclic VMS, improves sleep and premenstrual mastalgia, does not increase breast proliferation or cancer risk, increases bone formation and has beneficial cardiovascular effects [91]. In the anovulatory woman, progestogens help coordinate regular uterine shedding when given as a late luteal replacement treatment, on days 19–26 of the cycle [92]. The regimen, dose and type of progestogen used varies widely, with little consensus about the optimum treatment approach. In case of anovulatory bleeding medroxyprogesterone acetate (Provera) may be used [48], 10 mg per day for 10 to 14 days per month, but it requires caution in patients with severe hepatic dysfunction [47]. In case of endometrial hyperplasia without atypia medroxyprogesterone acetate may be indicated [93], 10 mg per day for 14 days per month (with caution in patients with severe hepatic dysfunction) or Megestrol (Megace) [94], 40 mg per day (also with caution in patients with severe hepatic dysfunction). In case of ovulatory bleeding medroxyprogesterone acetate can be indicated [95], 10 mg per day for 21 days per month, which represents an effective short-term therapy for decreasing heavy flow. It is not tolerated long term as well as levonorgestrel-releasing intrauterine system and demands caution in patients with severe hepatic dysfunction [47].

The prolonged use of high-dose progestogens can be associated with side effects, which include fatigue, mood changes, weight gain, nausea, bloating, oedema, headaches, depression, loss of libido, irregular bleeding and atherogenic changes in the lipid profile [9]. Progestogens administered from day 15 or 19 to day 26 of the cycle offer no advantage over other medical therapies such as danazol, tranexamic acid, nonsteroidal anti-inflammatory drugs (NSAIDs) and the IUS in the treatment of menorrhagia in women with ovulatory cycles [95]. Progestogen therapy for 21 days of the cycle results in a significant reduction in menstrual blood loss, although women found the treatment less acceptable than intrauterine levonorgestrel. This regimen of progestogen may have a role in the short-term treatment of menorrhagia [9].

The levonorgestrel releasing intrauterine system (LNG-IUS) is beneficial in the treatment of uterine fibroid, endometriosis, adenomyosis and endometrial hyperplasia [96]. It is a nonsurgical, long acting, alternative to the

traditional medical and surgical treatments for heavy menstrual bleeding [97] and represents an effective, better option for perimenopausal women requiring treatment for HMB [51]. In case of endometrial hyperplasia without atypia Levonorgestrel-releasing intrauterine system (Mirena) may be indicated [98], which can induce a 96% regression rate for hyperplasia without atypia [98]; this may cause irregular bleeding or amenorrhea. The contraindications include breast cancer, uterine anomaly that distorts the cavity, acute pelvic or cervical infection, and severe cirrhosis or liver cancer [90]. This treatment is more expensive initially, but similar to other therapies when averaged over five years [47]. In case of ovulatory bleeding Levonorgestrel-releasing intrauterine system can be indicated [84,95], with releases of 20 mcg per 24 hours.

Women with an LNG-IUS experience more progestogenic side effects compared to women having transcervical resection of the endometrium (TCRE) for treatment of their heavy menstrual bleeding, but there is no evidence of a difference in their perceived quality of life [84]. Age and fibroids are not predictive of treatment success with the LNG IUS [99] although women with genuine objective menorrhagia were more satisfied with the LNG IUS. Other benefits of the LNG IUS include fewer hot flushes compared with those having had a hysterectomy [100] and the ability to use it as the progestogen component of hormonal replacement therapy (HRT).

For the treatment of urogenital symptoms, in case of vaginal atrophy measures to prevent irritation of the vagina and to maintain the proper balance of flora are recommended. Vaginal moisturizers must be used regularly; the use of vaginal lubricants during sexual activity provides relief from vaginal dryness and irritation in a short period of time [6]. Topical estrogen therapy (with little systemic absorption or effects on the endometrium) effectively treats the symptoms of urogenital atrophy and restores the normal pH of the vagina, it reestablishes the normal flora of lactobacilli, increases the vaginal transudate and prevents the recurrence of urinary tract infections [101,102].

### *Surgical treatment*

Uterine artery embolization (UAE) is the complete occlusion of both the uterine arteries with particulate emboli and can be an effective and safe alternative in the treatment of menorrhagia and other fibroid-related symptoms in women not desiring future fertility [9].

The endometrial ablation (the surgical destruction of the endometrium) may be considered, if excessive uterine bleeding is unresponsive to medical intervention [103]. The endometrial ablation is less invasive than hysterectomy and preserves the uterus, although not fertility. The original "gold standard techniques" of laser, TCRE and rollerball ablation require direct hysteroscopic visualization of the uterus [9]. In appropriate candidates, non-hysteroscopic ablation techniques should be the ablation methods of choice in view of their higher efficacy and safety than

hysteroscopic techniques [52].

Traditionally, hysterectomy has been considered as the definitive surgical treatment for HMB but, even it has a 100% success rate due to complete cessation of menstruation and high levels of satisfaction [104], it is a major surgical procedure with significant physical complications and social and economic costs (high rate of major and minor post-operative complications, including, rarely, death and a long recovery time [105,106]. Hysterectomy should be considered only when medical management or endometrial ablation fails [107].

The management of uterine fibroids requires the complications of the fibroids to be balanced against the risks of treatment. Many women need no intervention for their fibroids and need only conservative treatment (medical treatment or surgical) [31]. In case of submucosal fibroids, menorrhagia may impose surgical resection [108]; alternatively, fibroids may be treated with uterine artery embolization.

In patients being treated for cancer, many therapies are gonadotoxic. The use of AMH serum levels as a biomarker of the growing follicle pool, in turn taken to reflect the ovarian reserve, in patients being treated for cancer is proving to be of increasing value in assessing ovarian function and advising patients before and after cancer treatment [109].

### *Alternative therapies and diet*

Searches for various alternative therapies in order to improve the quality of life is continuous, because the hormonal therapy can cause complications including malignancy (risk of neoplasia of the endometrium and possibly the breast) [110,111]. Some women use self-care strategies, including lifestyle modifications, complementary and alternative therapies, such as herbal preparations, exercise programmes and relaxation techniques. For example, lifestyle alterations for the amelioration of hot flashes can include measures regarding fight against obesity and smoking, exercise, relaxation techniques, and even acupuncture [112]. But the effectiveness of relaxation techniques in treating vasomotor symptoms and sleep disturbances remains debatable [113]. They are studies that proved the effectiveness of yoga therapy in managing the distressing perimenopausal symptoms [53]. Physical activity may be an effective way of significantly reducing the perimenopause-related symptoms, both the psychosocial and physical symptoms, and it improves quality of life [114,115].

Because of the positive association between perimenopausal symptoms with overweight/obesity, a healthy dietary pattern must not be neglected [42]. A Mediterranean-style dietary pattern decreases the incidence of insulin resistance and metabolic syndrome [116] and can reduce overweight/obesity. The body fat is possibly acting as a risk factor for VMS early in the menopause transition

[117] and an adverse adipokine profile is associated with more VMS, particularly early in the menopause transition [118]. Also, lower rates of VMS were reported in several studies of postmenopausal women who used soy isoflavone supplements (phytoestrogens) [119,120], but without showing a clear dose-response effect. Phytoestrogen treatment interventions have also shown time-limited positive effects on cognition, but data in humans are largely inconsistent and guidelines for the duration of isoflavone consumption are also required [121].

Classifying perimenopause status requires data that include age, smoking status, vasomotor symptoms, and cycle irregularities as predictors. Accurately identifying perimenopausal women may allow for early implementation of increased monitoring and/or interventions regarding lipids and central weight gain which may result in improved long-term outcomes [122]. The transition into perimenopause helps women to increase their health awareness and presents an opportunity to address modifiable risk factors and integrate healthy behaviours [123]. As women experience perimenopause, they adapt and learn to manage the health challenges associated with menopause [124].

### Conclusions

The endometrium histopathological study in perimenopausal women is mandatory, in cases of abnormal uterine bleeding. Detecting early atypical hyperplasia and endometrium cancer ensures an excellent prognosis.

We still need to improve the scientific accuracy of research regarding perimenopause. An improved correlation with age at time of treatment, individually given to women in correlation with their age, will assure better recommendations on the treatment efficacy.

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