Abnormal Vaginal Bleeding - practice guidelines in evaluation and management

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Abstract

Abnormal vaginal bleeding is a common cause of complaint for the women in reproductive age. In the management identifying possible causes is crucial in order to establish the right treatment strategy. Significant morbidity and mortality still might be associated with abnormal vaginal bleeding depending much on the cause and the severity of the bleeding. In the light of the large trials, and of the new minimal invasive approach in uterine pathology, this paper tries to get new insight into the management either medical or surgical for this condition.

Keywords: *bleeding, uterine, hormone therapy*

Management of abnormal vaginal bleeding

Initial assessment

Before starting any treatment should be ruled out all the possible causes and differential diagnosis for abnormal bleeding: pregnancy related (implantation, ectopic pregnancy, abortion, retained products of conception, placenta accreta, mola); hematologic (thrombocytopenia, platelet dysfunction, von Willebrand, factors deficiencies, coagulation disorders); Endocrine (Thyroid, Hyperprolactinemia, polycystic ovarian syndrome, adrenal, ovarian disorders); Infectious (cervicitis, pelvic inflammatory disease); Uterine pathology (polyp, fibroid, myoma, endometriosis, cervical dysplasia); Drugs (contraceptives, antipsychotics, anticoagulants, platelet inhibitors); Trauma (laceration, sexual abuse, foreign body, abortion related or other procedures); Other (excessive excercise, stress, eating disorders, systemic disease, intrauterine device).

Thus, family, social and sexual history, medical and surgical history as well as menstrual detailed history, are crucial.

After a complete history and review of systems, physical examination should always be carried to rule out the above mentioned possible causes begin with vital signs, with focus on anemia as well as other clues for underlying causes.

The laboratory and other studies should include initially pregnancy test (i.e. urine/blood test), complete blood cell count, pelvic ultrasound.

If bleeding is severe or underlying bleeding disorder is suspected, then the following should be measured: Prothrombin Time, partial thromboplastine time, bleeding time, platelet aggregation, von Willebrand panel, factor levels and activity.

In the case of suspected endocrine disorder: free thyroxine, thyroid-stimulating hormone, prolactin, total and free testosterone, Dehydroepiandrosterone sulphate, lutheizing hormone and follicle-stimulating hormone.

If infectious etiology is suspected then wet mount of discharge, gonorrhoea and chlamydia tests should be performed.

Medical treatment options

The medical treatment avoids the morbidity and mortality of surgery, but may have adverse effects and must be

continued. Though they are rare, randomized studies consisting of objective assessment of the menstrual flow bring the most accurate proofs for the success of the therapy.

Menorrhagia is the most frequent cause for iron deficiency anaemia in the developed countries. In many cases, the main syndrome accused by women with menorrhagia is fatigue.

Women who want to avoid the surgical treatment, though, may accept a larger flow if the anaemia is kept under control with iron supplements.

The goal of the medical treatment is the reduction of the menstrual flow less than 80 ml, the prevention of iron deficiency anaemia and the improvement of the quality of life.

The medical treatment in menorrhagia may be non-hormonal and hormonal. The choice of the treatment depends on various factors:

- The cause of the abnormal vaginal leak;
- The woman's age;
- Whether the woman wants to preserve her fertility;
- The menstruation characteristics (regular of not, dysmenorrhea);
- Possible contraindications;
- The patient's preferences.

It is important to inform the patient about the different treatment options, in order for her to make a documented choice. It has been proven that this action can modify the treatment choice and may also improve the results[3].

Non-hormonal treatment

Non-steroid anti-inflammatory treatments. The cyclooxygenase inhibitors are classified in:

- COX-1inhibitors (acetylsalicylic acid, indometacin, naproxen, ibuprofen, fenamates - mefenamic acid, flufenamic acid, mecofenamic acid);
- COX-2 inhibitors (celecoxib).

Most of the studies have concluded that the menstrual flow has been reduced among women who used COX-1 inhibitors compared to women who used placebo. Moreover, there is no data to prove that a NSAI (naproxen or mefenamic acid) is superior to other drugs[4]. Fenamates (e.g. mefenamic acid) are the most studied NSAI drugs. The reduction of the menstrual flow varies between 22 - 46% with this therapy. Regarding the long term therapy (one year), it has been proven that mefenamic acid is equally efficient[5]. The reduction of the menstrual flow has been assessed also for the other members of the NSAI family (naproxen, ibuprofen, sodium diclofenac and flurbiprofen). The reduction of the menstrual flow varies between 25-47% depending of the drug chosen and the dose used[4].

The NSAI must be considered as a first choice in the treatment of essential menorrhagia. The reduction of the menstrual flow is modest, but the NSAI are generally well tolerated for a long term treatment. Moreover, they are efficient enough in the women with IUD cooper-T. As well, the NSAI are efficient in redressing dysmenorrhea.

The anti-fibrinolytic drugs - the high level of fibrinolytic activity from the endometrium caused by the premenstrual rise of the tissue plasminogen activator would be a mechanism that explains menorrhagia.

The tranexamic acid, a synthetic derivate of lysine, has anti-fibrinolytic effect through the reversible blockage of the sites where lysine ties in the plasminogen and therefore blocks the degradation of the fibrin[6]. Some clinical studies show that at women with DUB the tranexamic acid 2-4.5 gr/24h for a period of 4-7 days reduces the menstrual flow with 35-59% on a range of 2-3 menstrual cycles. Its effect overcame placebo, the mefenamic acid, flurbiprofen, etamsylat and oral noretisteron given in the luteal phase[7].

Various studies show that there is not a high risk of thromboembolism following treatment with tranexamic acid. Therefore, the antifibrinolytic drugs are an efficient choice in treating menorrhagia and should be considered as a first line of treatment in DUB. In addition, the antifibrinolytic drugs are efficient for women with IUD cooper - T[6,7].

Etamsylate - the epsilon-caproic acid reduces the capillary fragility, but the mechanism thorough which this effect is made remains unknown. The studies measuring objectively the menstrual flow show that etamsylate is inferior to NSAI or antifibrinolytic drugs. In some countries (UK) this medicine is not prescribed[2].

Desmopressin (DDAVP) is a synthetic analogue of the organic vasopressin hormone. It has a well-known role in treating coagulation disorders (the von Willembrand disease, haemophilia A) due to its ability to induce a growth in the plasma densities of the von Willembrand factor (vWF) and of the VIII factors (FVIII). In cases where patients with the von Willembrand disease develop severe menorrhagia, the DDAVP is administrated intravenously by 0.3μg/kg, which will rapidly grow by 3 to 5 times the FVIII and vWF levels. In ambulatory cases, a nasal spray formula (150-300 μg) will be used. The first dose will be administrated during the first day of the menstruation and the other, the following day. Still, despite the positive results based on the subjective women testimonials, there are no randomized studies that support objectively the effect of nasal administration of this drug[8].

DDAVP stimulates the expression of the plasminogen tissue activator, the adherence of the platelets and the vessels constriction. These effects can explain the results of a study that showed the improvement of the menorrhagia caused by IUD to women treated with DDAVP tablets[8].

Hormonal Treatment

Progestatives are the most frequently used drugs prescribed to women with menorrhagia. The usage of progestatives is wrongly based on the fact that women with menorrhagia usually have anovulatory menstrual cycles and that progestatives coordinate the regular exfoliation when they are administrated as a supplement for the luteal phase in the days 15 - 26 of the cycle. Still, numerous studies have stated that women with (periodical) excessive regular bleeding have normal ovulatory cycles. Hence, the role and efficiency of using progestatives in treating all the inexplicable menorrhagia cases still remain debatable and there are few data in support of their usage.

The women with anovulatory DUB benefit from progestative therapy. Through their anti-proliferation effect, the progestatives stop the endometrial growth and induce a organized exfoliation of the endometrium after withdrawal[9].

Women with ovulatory DUB are not suitable to be prescribed cyclic progestatives for a short period of time (5-10 days)[10]. It has been shown that this administration would give a growth to the menstrual flow[11].

A meta-analysis from Cochrane Library on cyclic therapy with progesterone showed that administrating progestatives in the luteal phase is less efficient in reducing the menstrual flow in comparison with tranexamic acid, danazol and IUD with progesterone[12].

Still, longer periods of administration (5mg noretisteron 3 times/day in days 5-26 of the menstrual cycle) have produced a significant reduction in the menstrual flow (with 87%) when were compared with the flow before the treatment. However, the satisfaction rate of women that underwent this treatment was low: only 22% of them still wanted to continue the therapy after 3 cycles[13].

Higher dozes of progesterone (30 mg/24h) can be administrated in order to control the excessive bleeding. This treatment is usually effective in 24 to 48 hours. Progestatives, in pharmaceutical dozes, have a strong anti-estrogenic impact. In addition, they inhibit the synthesis of the estrogenic receptors and the oncogenes transcription induced by the estrogens. Through this anti-estrogenic effect the progestatives stabilize the endometrium, induce the stromal predecidualization and stop the bleeding. After this, the progesterone doses can be lowered and, in the end stopped. After a few days from the interruption there will be withdrawal caused bleeding.

The side effects of the oral progestatives vary depending on type, dose and duration of treatment. These include growth in weight, head aches, depression and symptoms similar to those of PMS..

Intrauterine administration

Inserting a IUD which contains copper maintains the menstrual cycle at a high flow, whereas inserting one impregnated with progesterone reduces the flow significantly. There are already two intrauterine systems impregnated with progesterone available on the market: one delivering levonorgestrel (LNG) on a period of ~5 years, and other which deliver progesterone on a period of ~ 16 months.

The LNG-IUS reduces the menstrual flow by 96% within a year[14]. After a period of 3 years 65% of the women with LNG-IUS continue to have improved menstrual bleeding. Besides reducing the menstrual flow, LNG-IUS can improve dysmenorrhoea and reduce the risk of getting the pelvic inflammatory disease. In addition, LNG-IUS delivers a very effective contraception, but in order to have this effect it must be introduced within the first 7 days of the menstrual cycle.

Because of the low levels of the progesterone in the blood, the systemic effects are minimal. The main side effect associated with LNG-IUS is intermittent uterine bleeding and the spotting, especially during the first months after the insertion. It is very important to inform the patient on the alterations in menstrual flow before the insertion of the LNG-IUS. This includes the possibility of having amenorrhea which can be an unwanted effect and also prohibited in some cultures and religions.

The estro-progestative combinations as combined contraceptive oral pills (CCO) are very often used in the excessive or irregular uterine bleeding management.

Through its proliferative effect, the estradiol induces o rapid growth of the endometrium in the denudated areas that do not respond to the stabilizing effects of the progestative. However there are few data (3-6 cycles duration and a adequate follow-up) that would scientifically sustain this assessment[16].

It is not clear if the formulas containing ethinyl-estradiol (E2) in a lower dozes are more efficient in reducing the menstrual flow than the chemicals with higher dozes of E2. In various studies there have been used dozes higher than 30-35 μg E2. Continuously administrating CCO on a short period of time can improve the excessive menstrual bleeding. A CCO that contains LNG/E2 cyclically administrated on more extended periods of time has produced a menstrual bleeding at every 3 months[17]. However, its prescription to patients with menorrhagia still remains to be evaluated.

Androgens

Danazol is a isoxazoline derivate of 17α-etinil-testosterone which takes action on the hypothalamus-hypophysis axe and endometrium levels, producing atrophy. It reduces the menstrual flow with 80%. The high dozes of danazol (≥ 200 mg/24h) are more efficient than the lower ones because of the inhibiting effect on the ovulation[2]. It seems to be a more efficient choice in treating excessive menstrual bleeding than other drugs (NSAI, oral progestatives and CCO). There are no randomized studies that compare danazol to the tranexamic acid or to LNG-IUS[18].

Even if the danazol has proven good results in treating menorrhagia, its clinical use is limited because of the androgenic side effects that have been developed to ~ 75% of the patients. Moreover, it may increase the cholesterol at abnormal plasmatic levels. During treatment with danazol, the patient should use mechanical contraceptive because of the high potential risk of virilism of the embryo if conceiving during treatment. Because of these side effects, danazol is limited to women that will proceed with surgical interventions and is limited as short term treatment to atrophy the endometrium before the endometrial destruction.

Gestrinone is a 19-testosterone derivate with antiprogestative, antiestrogenic and androgenic side effects. It is more efficient than placebo in reducing the menstrual flow to women exposed to excessive menstrual bleeding (with 79%)[19]. However, many women treated with this drug complain of getting excessive hairiness, weight gain, acne, which discourages long term treatment[2].

Gn-RH(Gn-RHa) Agonists administrated continuously or in depo can cause down-regulation at the Gn-RH receptors` level, that inhibits the secretion of the hypophysis gonatropines. The final result is the ovarian functions` suppression and a hypo-estrogenic status. Gn-RHA can be prescribed for various treatments such as treatment for excessive menstrual bleeding, but are mainly used to treat SVA associated with uterine fibroma. It frequently induces amenorrhea while also reducing the uterine volume by 40-60%[2,20].

Still, the hypoestrogenic status is responsible for significant side effects. The most important side effect is osteoporosis because of the reduction of estrogens in blood circulation. This is why the Gn-RH must not last for more than 6 months.

The side effects of Gn-RH administration are usually shown on a long term. However, they are very efficient when taken on a short period of time; example: preoperatory thinning of the endometri-

um or reducing the myomas before the myomectomy/hysterectomy. Similarly, the therapy with Gn-RH 2-3 months prior to the surgical treatment of the uterine fibroids reduces tumor size, the adverse effects and costs, and in some cases avoids hysterectomy.

Anti-progestatives - The Mifepriston (RU-486) is a synthetic 19- norsteroid with a anti- progestative action that inhibits ovulation and breaks the endometrium`s integrity. It was shown that administrating 5mg/day of RU-486 has a contraceptive effect and induces amenorrhea in most cases[21]. It was also used in the medical treatment of uterine fibroids[22]. Because its endometrial effect is reached without estrogenic withdrawal, it can be a promising alternative in the long term treatment of menorrhagia. However, there is need for clinical studies before using it in treating menorrhagia.

Particular cases

Acute and severe AVB - A severe metrorrhagia may sometimes cause patient's immediate admission. In such cases, after the diagnostic evaluation admission is required as for the following conditions:

- Hb < 8g/dl;
- the difference of systolic blood pressure every other 5 minutes after position change is > 10 mmHg or pulse increase is > 20 b/min;
- bleeding is profuse and persistent.

If there are signs of haemodynamic instability should be considered first therapy against hypovolemic shock (isotonic perfusions, plasma or, in extreme cases, integral blood transfusions), uterine curettage and/or therapy with high doses of estrogens.

Uterine curettage offers the immediate bleeding stop and allows for the necessary time for haemodynamic rebalancing and starting the medical treatment.

Oestrogen therapy (hormonal haemostasis) in high doses leads to endometrial proliferation, thrombocyte aggregation and the increase of the fibrinogen level and of factors V, IX. Therapy with high doses of estrogens shall be associated with antifibronolytics (tranexamic acid 2-4 gr/day and/or NSAIs and antiemetics (like Ondansetron) because it has nausea as side effect.

- Both administration methods (oral or intravenous) are equally efficient in stopping the bleeding. Intravenous method is chosen if the woman has an acute bleeding which calls for the immediate stop of the blood flow. If the bleeding does not stop in 12-14h with one of the above mentioned methods, then uterine curettage and endometrial biopsy are recommended.
- Both methods shall include therapy with progestatives for 5-7 days, and then the patient shall wait for a withdrawal bleeding. The progestatives which are mostly used for such purpose include Norethindrone (5 mg per os at 6h daily) or MPA (5-10 mg per os daily).
- After stopping the bleeding, the COC administration is continued (1tb/day) for 3-6 months.

Therapy with high doses of progestatieves is reserved for cases of excessive DUB, but less dramatic[24]. The used proegstatives are:

- MPA 20 mg/day;
- Noretindrone acetate 10 mg/day;
- Megestrol acetate 40 mg/day.

Withdrawal bleeding is expected at approximately 3 days after the last dose. After this, the above progestatives are administrated at half of initial dose for 10 days/month as support therapy.

The therapy failure requires a diagnostic reassessment and an endometrial biopsy. Bleeding from progestatives withdrawal suggests the absence of endometrial malign pathologies.

After stopping the acute event, which proves that AVB is a DUB, it is necessary to mention whether it is an anovulatory DUB or ovulatory DUB.

Oral contraception drugs. If however it is not a life-threatening bleeding, but the patient become anaemic, then minidoses of COC may be administrated (30-35 μg E2).

The last choice is hysterectomy that shall be indicated according to the above mentioned criteria.

DUB at teenage girls - 10 mg MPA, 10 days/month for at least 3 months would be the best choice. Mention should be made that screening of coaugulopathies is to be made, especially if the DUB is severe.

Table 1

Therapy with high doses of estrogens [23]

Intravenous method
25 mg conjugated estrogens /4h until bleeding stops.
Oral method
2.5 mg conjugated estrogens /4h until bleeding stops plus a sole dose for 7-10 days or
2 mg E2 micronised /4h until bleeding stops plus a sole dose for 7-10 days

Table 2

COC minidoses in acute menorragia [15,25,26]

Method 1
4 tablets/24h until flow stop (usually in the first 48h), then 3 tablets for 3 days + 2 tablets for 3 days and then 1 tablet per day for 21 days. After this, the withdrawal bleeding is expected
Method 2
1 tablet/6h until flow stops (usually in the first 48h) and then the dose is reduce by 1 tablet daily until obtaining a dose of 1 tb/day. After this, the withdrawal bleeding is expected. And after the flow finishes, minidoses of COC are administrated for 4-6 months
2 tablets daily for 5-7 days. After this, the withdrawal bleeding is expected

DUB at adult women - the long-term treatment for these patients depends on patient's option for contraception medication, ovulation induction or mere bleeding stop. If the patient only wishes to stop the DUB, 10 mg MPA 10 days per month for at least 6 months is the best choice. COC and Clomifen are administrated at women who still want contraception or ovulation stimulation.

DUB in perimenopause - It is not appropriate to cyclically administrate progestatives at women in perimenopause having DUB. In this case, the best solution is minidosed COC. An alternative choice would be administrating conjugated estrogens (0.625-1.25 mg) for 25 days, together with mg MPA (or another progestative) in days 15-25, after the exclusion of organic pathology.

Ovulatory DUB - The long-term treatment of ovulatory DUB with menorrhagia is more difficult. If organic abnormalities have been excluded, NSAI, progestatives, danazol or Gn-RHa may be administrated. Sometimes it is necessary to combine two or three of these drugs to stop the bleeding.

Surgical treatment

Surgery may be needed in order to solve lesions, such as polypi and fibroids. The surgeon has to be as conservative as possible in cases where the patients want to maintain their fertility. Surgery includes polypectomy, endometrial destruction, myomectomy and hysterectomy. Submucous myomas and endometrial polypi shall be solved hysteroscopically.

Hysterectomy - Considering the abdominal (AH), vaginal (VH) and the laparoscopically assisted vaginal hysterectomy (LAVH), the first one is the most common one. The last one has the advantage of short-time hospitalisation (24h), but it is not very spread in Romania.

Hysterectomy complications are underestimated sometimes. The mortality differs according to the development of the health system from 0.038 % in England to 0.1 % in USA.

Long-term injuries. Hysterectomy can be associated with anexectomy and it can be total or subtotal. Hysterectomy without anexectomy may induce ovarian failure prematurely increasing the risk of cardiovascular diseases and osteoporosis. Bilateral anexectomy (surgical menopause) may be extreme or symptomatic.

If a subtotal hysterectomy is performed, the sexual function is preserved better than in the case of total hysterectomy. However, cervical pathology screening (Babes-Papanicolaou test) shall be continued. In 7% of cases with subtotal hysterectomy, endometrial tissue is noticed[28]. The prevalence of sexual problems in the first 6 months after the surgery has been evaluated in a Danish study: 43% after VH, 41% after subtotal AH and 39% after AH[29].

Endometrial ablation

These methods have the advantage of a shorter hospitalization period (less than 24 hours) as compared to VH or AH (a few days of hospitalisation). As hysterectomy, these methods shall be recommended to women who do not want fertility preservation.

There are some related complications to the procedure: amenorrhea, failure increased by adenomiosis for first generation procedures, low intra-surgical complications (1%) like bleeding, perforation, the necessity of emergency operation and the absorption of dystension substance, except thermal endometrial ablation through radiofrequency, microwaves and thermal balls do not use dystensia substances.

Endometrial ablation methods:

First generation

Trans Cervical Resection of the Endometrium (TCRE)

Endometrial Laser Resection (ELA)

Roller Ball Endometrial Ablation (REA)

Second generation

Thermal Balloons (Thermachoice, Cavatherm)

Microwave Endometrial Ablation (MEA)

Hydrothermal Ablation

Cryotherapy

Patients treated with endometrial ablation need sometimes (~21% of cases) a second surgical intervention (hysterectomy)[30,31]. No serious differences have been noticed between the results of the first and second generation methods (bleeding, satisfaction and life quality) and the rate for the second surgical intervention necessity. The second generations methods require a shorter intervention time and are associated to less adverse effects[32].

The rate of pregnancy after endometrial ablation is very low (0.7%). A pregnancy after endometrial ablation has a high risk for the foetus. Women that underwent endometrial ablation shall use effective contraception.

Conclusions:

Currently a large variety of medical and surgical tools are available in treatment of abnormal vaginal bleeding.

Hysterectomy continues to be the definitive therapy for the patients who are not assisted by other methods.

Best treatment is not only based on identifying the cause and stopping the bleeding regardless to method, therefore the specialist should take into account the patient's desire for preserving menstruation, fertility as well as increasing the quality of life and the long term consequences. ■

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Menopauza terapie naturală fără riscuri

Dr. Oana Gagionea

Menopauza este o perioadă fiziologică prin care fiecare femeie va trece la un moment dat. Simptomatologia psihică şi vegetativă asociată menopauzei se datorează unei producţii scăzute de hormoni ovarieni. Aceste modificări aduc adesea suferinţe considerabile şi afectează calitatea vieţii pacientei. Medicul de multe ori este nevoit să înceapă un tratament medicamentos. Tratamentul de substituţie hormonală are un efect pozitiv asupra simptomatologiei, însă, în mod frecvent, este tulburat de efecte secundare şi riscuri crescute sau chiar şi contraindicaţii. Din ce în ce mai mulţi medici au o părere foarte rezervată despre terapia de substituţie hormonală, având în vedere în special incidenţa crescută a tumorilor maligne hormon-dependente.

Tratamentul tulburărilor de climax cu medicamente non-hormonale poate fi indicat în pre-, peri- şi port-menopauză timpurie, când ovarele încă mai produc cantităţi mici de hormoni.

În multe din aceste cazuri, Klimaktoplant oferă o alternativă non-hormonală, naturală, cu risc scăzut şi fără contraindicaţii.

Klimaktoplant este un preparat homeopat standardizat, ce conţine patru remedii, fiecare cu modul său diferit de acţiune, ce produc un efect sinergic asupra tulburărilor somatice şi psihice ale menopauzei. Cimicifuga racemosa este un remediu utilizat pentru dereglări de natură ginecologică de peste 200 ani.

Autorii Jarry şi Harnischfeger au demonstrat capacitatea diferitelor părţi ale extractului de Cimicifuga de a se conecta la receptorii de estrogen şi de a reduce selectiv concentraţia în ser a hormonului pituitar LH.

Experienţa clinică confirmă eficienţa Klimaktoplant în tratamentul simptomelor complexe de deficienţă de climacteriu în sfera somatică, psihică, neuro-vegetativă şi organică. Raportul pozitiv între riscuri şi beneficii (efecte secundare scăzute specifice substanţelor, fără contraindicaţii) desemnează de asemenea Klimaktoplant pentru terapia pe termen lung, fără hormoni şi cu risc scăzut. ■

VAVIAN PHARMA

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