

DR DRAŽEN POSTRUŽNIK M.D. OBGYN



**BRIJUNI
2015**

ZAGREB, CROATIA

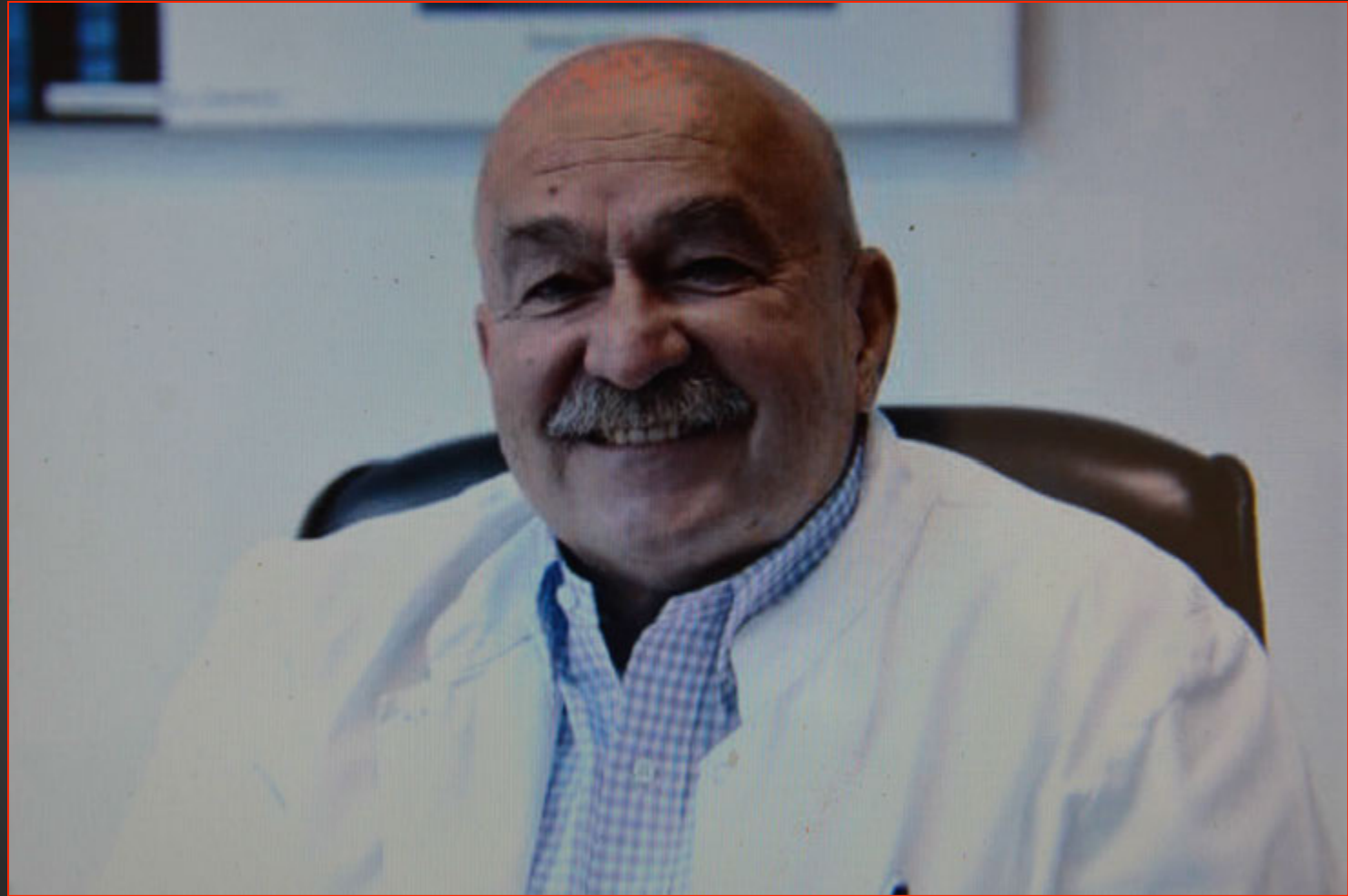
NICE, FRANCE

MONTE CARLO, MONACO

ABNORMAL UTERINE BLEEDINGS



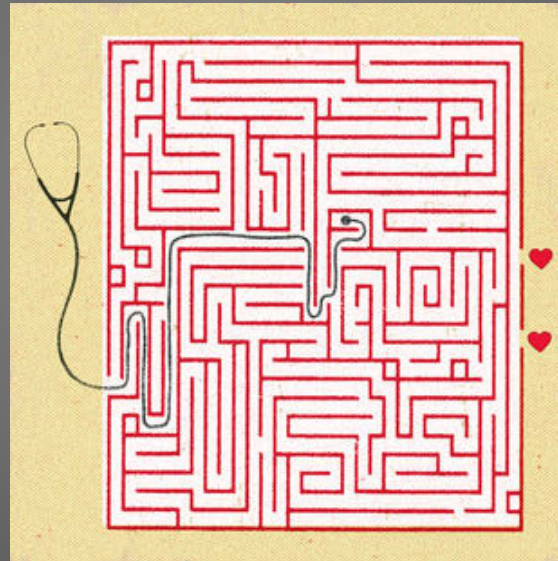




A.U.B.

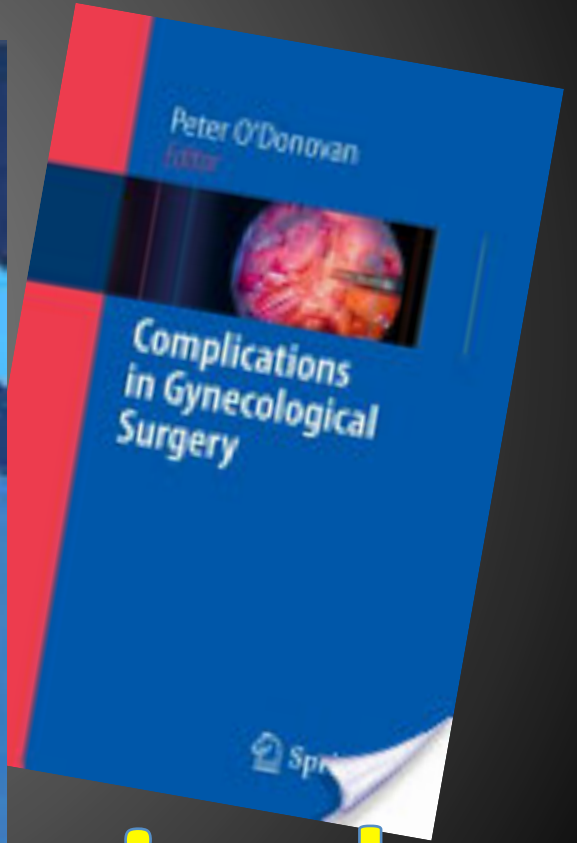
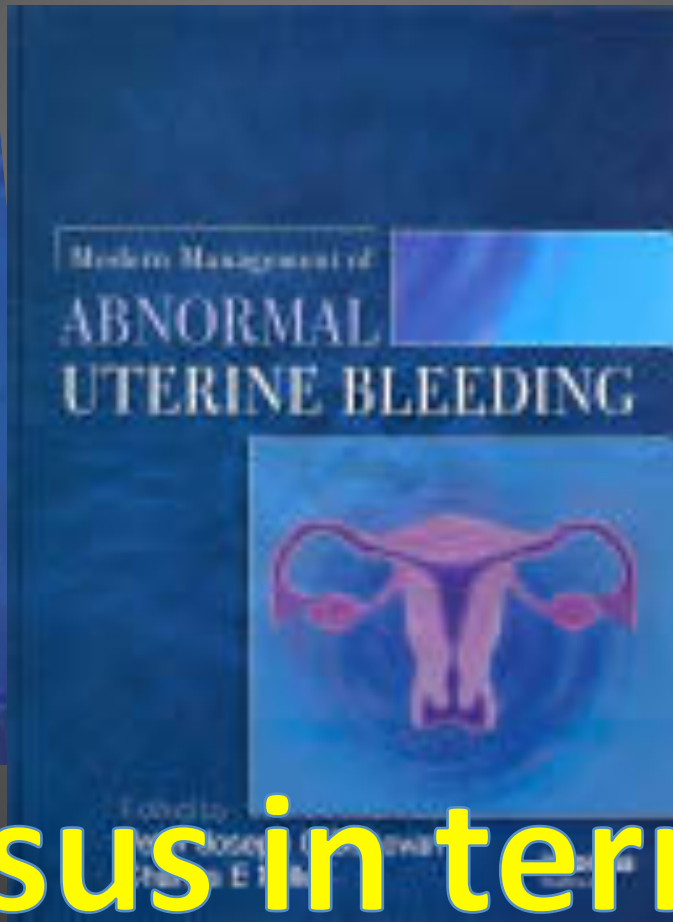
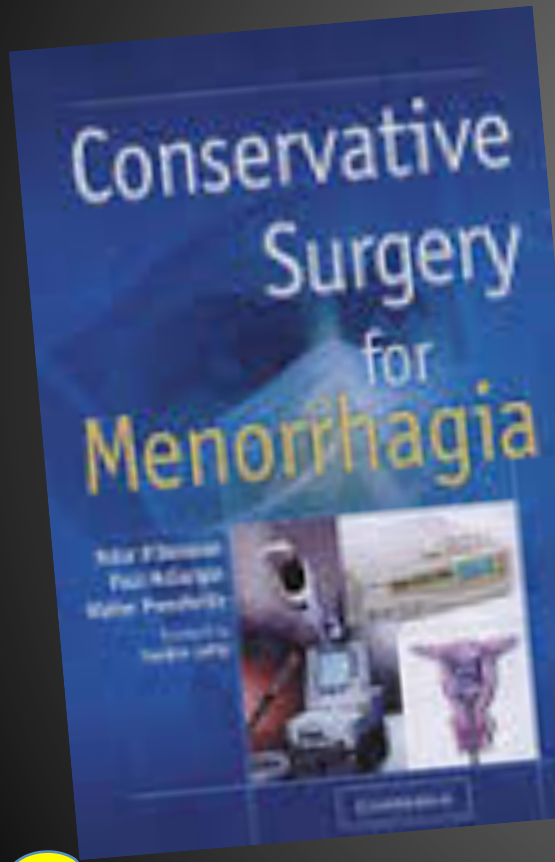
VS

LESS
AGGRESSIVE
MEDICATION



SURGERY

D.U.B. = A.U.B.



Consensus in terminology

A.U.B.

30% in reproductive age
50% in perimenopause

A.U.B.

Disfunction:

Ovulatory 20%

Anovulatory 80%

**CAUSES OF AUB
(differential
analysis
and diagnosis)**

Endocrine causes

- Cushing's disease
- Immature hypothalamic-pituitary axis
- Hyperprolactinemia
- Hypothyroidism
- Menopause
- Obesity
- PCOD
- Premature ovarian failure

Structural lesions

- Adenomyosis
- Coagulopathies
- Condyloma accuminata
- Dysplastic or malignant lesions of cervix or vagina
- Endometriosis
- Endometrial cancer
- Uterine or cervical polyps
- Uterine leiomyomata
- Trauma

Infections

- Chlamidia
- Gonorrhoea
- PID


Medications

- Hormonal agents
- Low dose OCs
- IUD
- NSAIDs
- POP ("mini pill")
- Tamoxifen
- Warfarin

Pregnancy

- Ectopic pregnancy
- Incomplete abortion
- Pregnancy complications

Risk factors for endometrial cancer (RR = relative risk)

Age - 75% of cases occur after menopause with peak incidence in the late 60s.	RR (age > 60 years) = 5.2	
Obesity - especially upper body fat. This may be secondary to increased estrogen production and bioavailability.	RR= 3 to 10	
Polycystic ovary disease.	RR = 5.2	
Unopposed exogenous estrogen.	RR = 2 to 14	
When progestins are added (oral contraceptives or with replacement therapy), relative risk is less than for the general population.	RR= 0.5 to 1	
Diabetes (all types grouped).		
Personal or family history of ovarian or breast cancer. Women who are overweight and have had breast cancer are at even greater risk.	RR = 2 to 2.8	
Nulliparity.	RR = 1.3	
Late menopause.	RR entering menopause after age 52 = 2.5	
Tamoxifen therapy - Use for greater than one year is an independent risk factor.	RR = 7.5	

A.U.B.

P.A.L.M. – C.O.E.I.N.

Basic FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age

Polyp
Adenomyosis
Leiomyoma (submucosal or other)
Malignancy & hyperplasia

Coagulopathy
Ovulatory dysfunction
Endometrial
Iatrogenic
Not yet classified

FIGO 2011



A.U.B.

Iatrogenic causes:

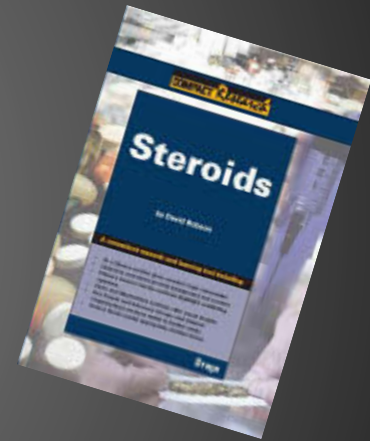
-COC

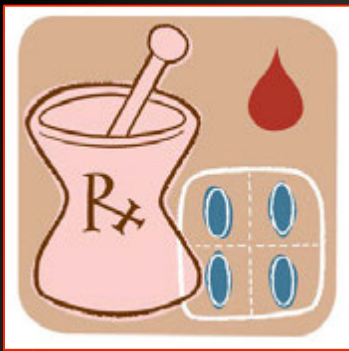
-HT

-Steroids

-Psychofarmaca (ovulation blocked)

-Tamoxifen





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Treatment

Progestins	70%-80%	dydrogesterone	20mg/day
		MPA	10mg/day
		NomAc	5 mg/day
		(cyclic continuous)	6 months
COC	30%-40%	EE,E2V,E2	6-12 months
		DNG,LNG,GSD,DRSP, NomAc	
IUD	10%-20%	{LNG}	5 years
UPA	10%-20%		5mg/10mg 3-6-9 months

CLASSIFICATION OF PROGESTINS

PROGESTERONE

Progesterone

RETROPROGESTERONE

Dydrogesterone

NONSTEROIDAL PR agonist

Tanaproget

PROGESTERONE DERIVATED

17-OH-progesterone
derivated

19-norprogesterone
derivated

PREGNANES

- Hydroxyprogesterone caproate
- Hydroxyprogesterone heptanoate
- Gestonorone caproate
- Chlormadinone acetate
- Medrogestone
- Medroxyprogesterone acetate
- Cyproterone acetate

NOR-PREGNANES

- Nomegestrol acetate
- Demegestone
- Promegetone
- Nestorone
- Trimegestone

Related to progesterone

SPIRONOLACTONE DERIVATED

Drospirenone

TESTOSTERONE DERIVATED

ESTRANES

- Lynestrenol
- Levonorgestrel
- Norethisterone
- Norethisterone acetate
- Ethinodiol diacetate
- Norgestrienone
- Dienogest

GONANES

- Norgestrel
- Desogestrel
- Gestodene
- Norgestimate

Related to testosterone

A.U.B.

Treatment - surgical

-Hysteroscopy

-Laparoscopy

-Laparotomy

*endometrial ablation

*polypectomy

*myomectomy

ovarian cyst resection

hysterectomy



Treatment

Hysterectomy remains the most absolutely curative treatment for DUB. Elective hysterectomy has a mortality rate of six per 10,000 operations. One randomized study found that hysterectomy was associated with more morbidity and much longer

hysterectomy was associated with more morbidity and much longer healing times than endometrial ablation

problems with sexual functioning. ³⁴ It still remains a popular method of treating DUB, especially in industrialized countries.

1. Neese RE. Abnormal vaginal bleeding in perimenopausal women. *Am Fam Physician* 1989; 40:185-92.
2. Bayer SR, DeCherney AH. Clinical manifestations and treatment of dysfunctional uterine bleeding. *JAMA* 1993; 269:1823-8.
3. Baughan DM. Changes in the management of patients with dysfunctional uterine bleeding. *Fam Pract Recertification* 1993; 15:68-78.
4. Prior JC, Ho Yuen B, Clement P, Bowie L, Thomas J. Reversible luteal phase changes and infertility associated with marathon training. *Lancet* 1982; 2:269-70.

Endometrial biopsy (EMB)

is the most commonly used diagnostic test for DUB.

It provides an adequate sample for diagnosis of endometrial problems in 90% to 100% of cases,^{1,2} but may fail to detect polyps and leiomyomas.

It is indicated in all women with DUB who are 35 years of age or older, since their risk of developing malignancy is much higher. Any

Endometrial biopsy may fail to detect polyps and leiomyomas.

1. Goldschmit R, Katz Z, Blickstein I, Caspi B, Dgani R. The accuracy of endometrial Pipelle sampling with and without sonographic measurement of endometrial thickness. *Obstet Gynecol* 1993; 82:727-30.

2. Stovall TG, Ling FW, Morgan PL. A prospective randomized comparison of the Pipelle endometrial sampling device with the Novak curette. *Am J Obstet Gynecol* 1991; 165:1287-9.

3. Johnson CA. Making sense of dysfunctional uterine bleeding. *Am Fam Physician* 1991; 44:149-57

Management of Acute Abnormal Uterine Bleeding in Nonpregnant Reproductive-Aged Women

Initial evaluation of the patient with acute abnormal uterine bleeding should include a prompt assessment for signs of hypovolemia and potential hemodynamic instability.

The etiologies of acute abnormal uterine bleeding should be classified using the PALM–COEIN system.

Medical management : Options include intravenous conjugated equine estrogen, multi-dose regimens of combined oral contraceptives or oral progestins, and tranexamic acid. Decisions should be based on the patient's medical history and contraindications to therapies.

Surgical management should be considered for patients who are not clinically stable, are not suitable for medical management, or have failed to respond appropriately to medical management. The choice of surgical management should be based on the patient's underlying medical conditions, underlying pathology, and desire for future fertility. Once the acute bleeding episode has been controlled, transitioning the patient to long-term maintenance therapy is recommended.

Management of Acute Abnormal Uterine Bleeding in Nonpregnant Reproductive-Aged Women

Acute AUB refers to an episode of heavy bleeding that, in the opinion of the clinician, is of sufficient quantity to require immediate intervention to prevent further blood loss.

Acute AUB may occur spontaneously or within the context of chronic AUB (abnormal uterine bleeding present for most of the previous 6 months).

~~The general process for evaluating patients who present with acute AUB can be approached in three stages:~~

- 1) assessing rapidly the clinical picture to determine patient acuity,
- 2) determining most likely etiology of the bleeding, and
- 3) choosing the most appropriate treatment for the patient.

Management of Acute Abnormal Uterine Bleeding in Nonpregnant Reproductive-Aged Women

Once the acute episode of bleeding has been controlled, multiple treatment options are available for long-term treatment of chronic AUB. Effective medical therapies include the levonorgestrel intrauterine system, OCs (monthly or extended cycles), progestin therapy (oral or intramuscular), tranexamic acid, and nonsteroidal anti-inflammatory drugs (6). If a patient is receiving IV conjugated equine estrogen, the health care provider should add progestin or transition to OCs. Unopposed estrogen should not be used as long-term treatment for chronic AUB.

Patients with heavy or unexpected bleeding disorders may respond to the hormonal and nonhormonal treatments. The treatment should be individualized based on the patient's history, physical examination, and laboratory studies. The treatment should be aimed at controlling the bleeding and restoring the patient's health. The treatment should be aimed at controlling the bleeding and restoring the patient's health. The treatment should be aimed at controlling the bleeding and restoring the patient's health.

**Effective medical therapies include:
the levonorgestrel intrauterine system,
OCs (monthly or extended cycles),
progestin therapy (oral or intramuscular), tranexamic
acid,
and nonsteroidal anti-inflammatory drugs**

Patients with bleeding disorders or platelet function abnormalities should avoid nonsteroidal anti-inflammatory drugs because of their effect on platelet aggregation and their interaction with drugs that might affect liver function and the production of clotting factors (17).

A.U.B.

Treatment

Acute AUB

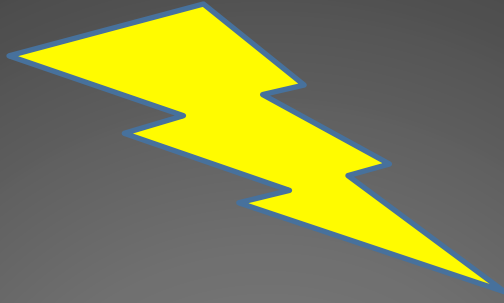
E+P, UPA, GnRH

Chronic AUB

progestins, COC, IUD (LNG),
UPA, NSAID

SURGERY

-primary (!)
-initial therapy failure



In practice:

In about 50% of (all)patients
surgery is finally applied

ABNORMAL UTERINE BLEEDINGS - CONSENSUS



AUB in different
countries of the world

BRIJUNI 2015



Conclusions and Recommendations

Based on the available evidence and expert opinion, the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice makes the following conclusions and recommendations:

The etiologies of acute AUB should be classified based on the PALM–COEIN system: Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory

**The etiologies of acute AUB
should be classified based on
the PALM–COEIN system**

future fertility.

Once the acute bleeding episode has been controlled, transitioning the patient to long-term maintenance therapy is recommended.



USA

2015

Conclusions and

Based on the The severity of bl response to med available evidenc Gynecologists' Co recommendation

The etiologies of Adenomyosis, Le dysfunction, End Medical manage appropriate. Opt oral progestins, a history and contr The need for surg bleeding, contrai medical management, and the underlying. surgical modality should be based on the aforementioned factors plus the patient's desire for future fertility.

Once the acute bleeding episode has been controlled, transitioning the patient to long-term maintenance therapy is recommended.

The need for surgical treatment is based on the clinical stability of the patient, the severity of bleeding, contraindications to medical management, the patient's lack of response to medical management, and the underlying medical condition of the patient

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Table Testing for the Evaluation of Patients With Acute Abnormal Uterine Bleeding

Laboratory Evaluation

Initial laboratory testing

Initial laboratory evaluation for disorders of hemostasis

Initial testing for von Willebrand disease*

Other laboratory tests to consider

Specific Laboratory Tests

- Complete blood count
- Blood type and cross match
- Pregnancy test
- Partial thromboplastin time
- Prothrombin time
- Activated partial thromboplastin time
- Fibrinogen
- von Willebrand factor antigen[†]
- Ristocetin cofactor assay[†]
- Factor VIII[†]
- Thyroid-stimulating hormone
- Serum iron, total iron binding capacity, and ferritin
- Liver function tests
- Chlamydia trachomatis*

*Adult women who receive positive results for risk of bleeding disorders or who have abnormal initial laboratory test results for disorders of hemostasis should undergo testing for von Willebrand disease. Adolescents with heavy menses since menarche who present with acute abnormal uterine bleeding also should undergo testing for von Willebrand disease.

[†] Consultation with a hematologist can aid in interpreting these test results. If any of these markers are abnormally low, a hematologist should be consulted.

Data from James AH, Kouides PA, Abdul-Kadir R, Dietrich JE, Edlund M, Federici AB, et al. Evaluation and management of acute menorrhagia in women with and without underlying bleeding disorders: consensus from an international expert panel. *Eur J Obstet Gynecol Reprod Biol* 2011;158:124–34; National Heart, Lung, and Blood Institute. The diagnosis, evaluation, and management of von Willebrand disease. NIH Publication No. 08-5832. Bethesda (MD): NHLBI; 2007. Available at <http://www.nhlbi.nih.gov/guidelines/vwd/vwd.pdf>. Retrieved December 5, 2012; and Diagnosis of abnormal uterine bleeding in reproductive-aged women. Practice Bulletin No. 128. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2012;120:197–206.



Conclusions: Abnormal Uterine Bleeding Is A Common And Sometimes Debilitating Condition In Women Of Reproductive age. Standardization Of Related terminology, A Systematic Approach To Diagnosis And investigation, And A step-wise Approach To intervention Necessary .Treatment Commencing With Medical Therapeutic Modalities Followed By The Least Invasive Surgical Modalities Achieving Results Satisfactory To The Patient Is The Ultimate Goal Of All Therapeutic interventions

A step-wise Approach To interventions



Recommendations

8.

Endometrial biopsy should be considered in bleeding women over age 40 or in those with bleeding not responsive to medical therapy, as well as in younger women with risk factors from endometrial cancer. (II-2A)

9.

Office endometrial biopsy should replace dilation and uterine curettage as the initial assessment of the endometrium for these women. (II-2A)

10.

Focal lesions of the endometrium that require biopsy should be managed through hysteroscopy-guided evaluation.

Summary Statements

6.

Once malignancy and significant pelvic pathology have been ruled out, medical treatment is an effective first line therapeutic option for abnormal uterine bleeding. (I)

7.

Medical treatment tailored to the individual woman's therapeutic goals, desire for contraception, underlying medical conditions, and tolerance of side effects will encourage compliance and maximize the likelihood of treatment success.

Once malignancy and significant pelvic pathology have been ruled out, medical treatment is an effective first line therapeutic option for abnormal uterine bleeding.



NSAID

COC

MPA

IUD-LNG

Danazol

GnRH agonists



Recommendations

2015

11.

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. (I-A)

12.

Combined oral contraceptive pills, depot medroxyprogesterone acetate, and levonorgestrel-releasing intrauterine systems significantly reduce menstrual bleeding and should be used to treat women with abnormal uterine bleeding who desire effective contraception. (I-A)

13.

Cyclic luteal-phase progestins do not effectively reduce blood loss and therefore should not be used as a specific treatment for heavy menstrual bleeding. (I-E)

14.

Danazol and gonadotropin-releasing hormone agonists will effectively reduce menstrual bleeding, and may be used for scenarios in which other medical or surgical treatments have failed or are contraindicated. (I-C).

15.

Patients receiving a gonadotropin-releasing hormone agonist for longer than 6 months should be prescribed add-back hormone therapy, if not already initiated with gonadotropin-releasing hormone agonist commencement. (I-A)



Conclusions

Women who have problematic irregular or heavy cyclic menstrual bleeding have a number of treatment options available that are supported by systematic review of the research literature. These include high strength of evidence that COCs can improve menstrual regularity for women with irregular bleeding patterns. Metformin is supported by moderate strength of evidence for improving cycle regularity especially among women with PCOS. This provides both a contraceptive and a noncontraceptive option for irregular menses. Other interventions like progestogens are associated with statistically and clinically meaningful improvements from baseline patterns, however the overall evidence is insufficient from well-designed, larger studies with ability to directly compare treatment arms rather than only pre-post measures within groups.

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**COC, progestins, IUD-LNG, TXA, NSAID....
and metformin (younger women with PCOD)**

e

ults

from COC and NSAID comparisons suggest comparable effectiveness. Not all women will benefit from these interventions. Across agents data are sparse to evaluate long-term improvements and risk of harms. Limitations include a predominance of small, short trials lacking standard terminology and diagnostic criteria for identifying and including women with AUB. Tools for collecting outcome data are crude (collection of sanitary products) and may contribute to a high rate of attrition. Biologic outcomes, like measured blood loss and hemoglobin or hematocrit levels, may neglect the importance of patient-reported outcomes that assess whether symptoms are considered resolved by women themselves. Nevertheless, the variety of effective options suggests many women can achieve symptom relief and have available choices that address both symptoms and contraceptive or fertility desires, as well as potentially improving other symptoms like menstrual cramping.

Italia



. Conclusione

Un gruppo internazionale di clinici-ricercatori con vasta esperienza di AUB ha trovato un accordo consensuale su un sistema di classificazione che facilita gli studi multicentrici su epidemiologia, eziologia e terapia delle donne con sanguinamento uterino anomalo acuto o cronico. Il sistema dovrebbe dare impulso anche alla realizzazione di meta-analisi di trials clinici ben disegnati e adeguatamente riportati. Si riconosce che il sistema necessita di periodici aggiornamenti e, al bisogno, di una sostanziale revisione, al passo con l'evoluzione delle conoscenze e della tecnologia e la crescente disponibilità di opzioni diagnostiche nelle diverse aree geografiche. Pertanto, raccomandiamo una revisione sistematica del sistema, programmata a

che ha già approvato
Editori e comitati
"materiali", "met
classificazione pro
Conflitto di interesse

Point is on technological and methodological improvements

e internazionale come la FIGO,

scritti sull'AUB le sezioni
tenendo conto del sistema di

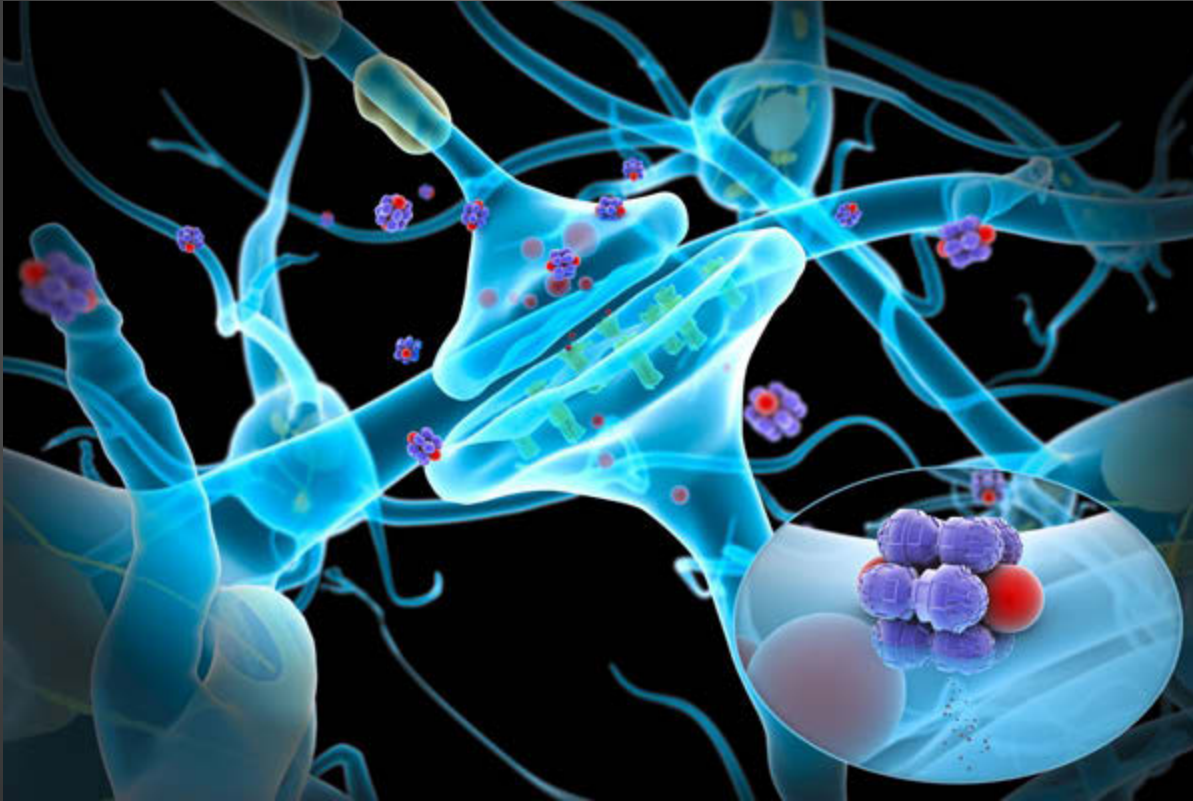
MMG, CHOD e FIS sono stati consulenti, hanno tenuto conferenze e ricevuto compensi da Bayer Schering Pharma, che ha in parte finanziato questa iniziativa (come segnalato nelle pubblicazioni di maggior rilievo). Numerose altre organizzazioni e società hanno contribuito, direttamente o indirettamente, allo sviluppo del progetto. Anche questi contributi sono esplicitamente segnalati nelle pubblicazioni di maggior rilievo. L'intero progetto è stato approvato dalla FIGO e dal suo Gruppo di Lavoro sui Disordini Mestruali.

(Traduzione di Alessandro Maturo, "Sapienza" Università di Roma)

France – the land of progestins !



Caractéristiques du traitement progestatif

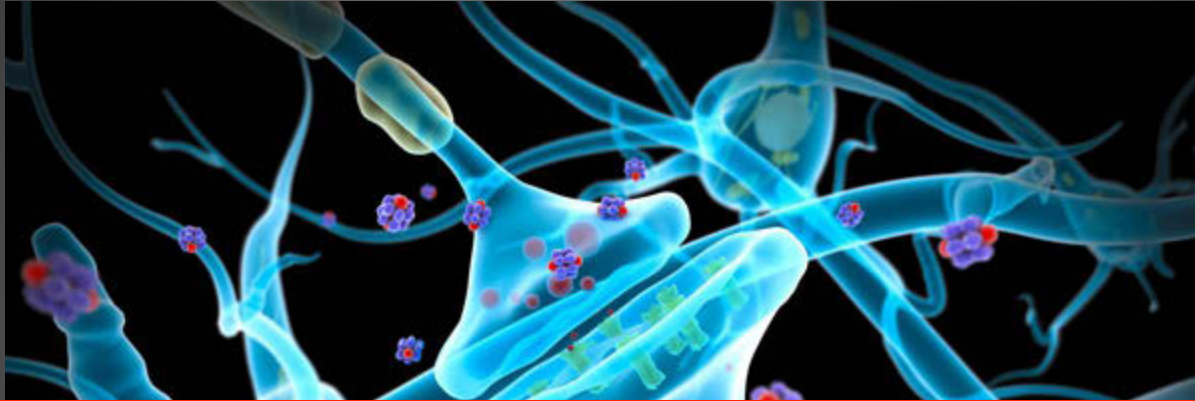


Pour chaque patient élaborer un plan individuel de prise de certains médicaments.
Gynécologue de surveillance obligatoire considérée, et, si nécessaire – et un
endocrinologue.

France – the land of progestins !



Caractéristiques du traitement progestatif



A long list of progestins, almost exclusively progesterone derivatives.

Beside gynecological survey of AUB, endocrinologist is often in the medical team. Individualisation!

Pour chaque patient élaborer un plan individuel de prise de certains médicaments.
Gynécologue de surveillance obligatoire considérée, et, si nécessaire – et un endocrinologue.

Overall

New ground breaking International Federation of Gynecology and Obstetrics's classification of abnormal uterine bleeding: Optimizing management of patients

There is considerable worldwide confusion in the use of terminologies and definitions around the symptom of abnormal uterine bleeding (AUB), and these are increasingly leading to difficulties in setting up multinational clinical trials and in interpreting the results of studies undertaken in single centers. In November 2010, the International

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Put an end to worldwide confusion in the use of terminology – PALM-COEIN definition

developed in response to concerns about the design and interpretation of basic science and clinical investigation that relates to the problem of AUB.



Overall

New ground breaking International Federation of Gynecology and Obstetrics's classification of abnormal uterine bleeding: Optimizing management of patients

The PALM group

The PALM categories refer to discrete (structural) entities that can be measured visually with imaging techniques, such as ultrasound, or histopathology testing. The “polyp” category lends itself to the clinical or investigative use based on a combination of location, number, and morphology. The PALM group is subdivided into patients with at least 1 submucosal polypoid lesion protruding into the endometrial cavity. Within the PALM group, it was proposed that the use of the term “polyp” for benign, hyperplasia, endometrial malignant or premalignant lesions, and leiomyosarcoma. The PALM group is further described with use of the FIGO classification and staging systems.

**PALM group:
Structural entities**

**COEIN group:
“iatrogenic” category**

The COEIN group

In contrast to the PALM group, the COEIN group includes non-structural entities that are not defined on imaging or histopathology testing. The “iatrogenic” category refers to AUB associated with the use of exogenous gonadal steroids, intrauterine systems or devices, or other systemic or local agents.



Overall

Practical tips

Dysfunctional uterine bleeding is a diagnosis of exclusion: other conditions such as uterine fibroids, endometrial polyps, and systemic diseases must be excluded by

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Only 2% of endometrial carcinomas occur before age of 40, leaving us a quite secure space for non-aggressive treatments.

s for

esity,

and polycystic ovary syndrome are risk factors

Postmenstrual scans are often useful; the endometrium should be at its thinnest then, and polyps and cystic areas are more noticeable



A.U.B.

VS

LESS
AGGRESSIVE
MEDICATION



SURGERY

CHOICE OF
OPTIMAL
APPROACH

**THANK YOU VERY MUCH
FOR YOUR KIND ATTENTION !**



HVALA NA POZORNOSTI !