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AUB in adolescenza:

management e diagnosi differenziale

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Fisiologia

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

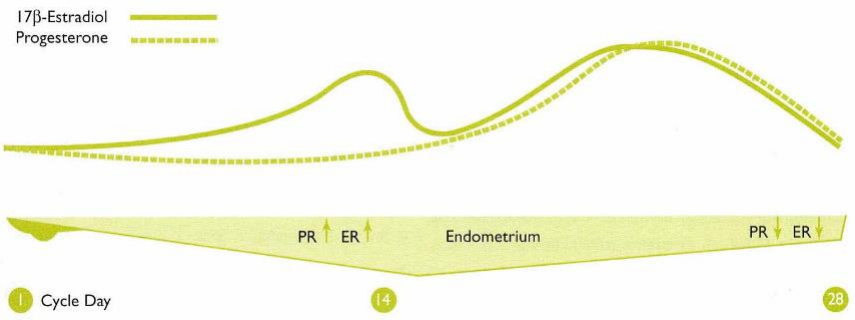
COMMITTEE OPINION

Number 651 • December 2015 *(Replaces Committee Opinion 349, November 2006)*

Committee on Adolescent Health Care

The American Academy of Pediatrics endorses this document. This document reflects emerging concepts on patient safety and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Menstruation in Girls and Adolescents: Using the Menstrual Cycle as a Vital Sign



Box 1. Normal Menstrual Cycles in Adolescent Girls ⇦

Menarche (median age):	12.43 years
Mean cycle interval:	32.2 days in first gynecologic year
Menstrual cycle interval:	Typically 21–45 days
Menstrual flow length:	7 days or less
Menstrual product use:	Three to six pads or tampons per day

AUB: terminologia

Educational series on women's health issues, 2006

"Excessive menstrual bleeding and that which occurs outside of normal cyclic menstruation is generally described as abnormal uterine bleeding (AUB). A menstrual pattern of reduced frequency or bleeding volume is also described as AUB.
Thus the term AUB is broad and inclusive of many possible underlying causes for the bleeding. It is reflective of a symptom or sign with many possible etiologic bases. When AUB cannot be attributed to an anatomic, organic, or systemic lesion or disease, it has traditionally been referred to as dysfunctional uterine bleeding (DUB)."

FIGO Working Group on Menstrual Disorders, 2011

No more DUB/ menorrhagia/ metrorrhagia
- AUB:
  – Heavy menstrual bleeding AUB/HMB
  – Intermenstrual bleeding AUB/IMB

AUB: eziologia

FIGO
INTERNATIONAL FEDERATION OF GYNECOLOGY & OBSTETRICS

Abnormal uterine bleeding:
- Heavy menstrual bleeding (AUB/HMB)
- Intermenstrual bleeding (AUB/IMB)

PALM—structural causes:
Polyp (AUB-P)
Adenomyosis (AUB-A)
Leiomyoma (AUB-L)
  Submucosal leiomyoma (AUB-LSM)
  Other leiomyoma (AUB-LO)
Malignancy and hyperplasia (AUB-M)

COEIN—nonstructural causes:
Coagulopathy (AUB-C)
Ovulatory dysfunction (AUB-O)
Endometrial (AUB-E)
Iatrogenic (AUB-I)
Not yet classified (AUB-N)

FIGO Working Group on Menstrual Disorders, 2011

AUB: eziologia

- Anovulatory uterine bleeding
- Pregnancy-related problems
  - Threatened, spontaneous, incomplete, missed abortion
  - Problems with termination procedures
  - Ectopic pregnancy
  - Gestational trophoblastic disease
- Infection
  - Pelvic inflammatory disease
  - Endometritis
  - Cervicitis
  - Vaginitis
- Vaginal abnormalities
  - Carcinoma
  - Lacerations
- Cervical problems
  - Cervicitis
  - Polyp
  - Hemangioma
  - Carcinoma
- Uterine problems
  - Submucous myoma
  - Congenital anomalies
  - Polyp
  - Carcinoma
  - Intrauterine device
  - Intermenstrual bleeding
  - Ovulatory bleeding
- Blood dyscrasia
  - Thrombocytopenia
  - Clotting disorders
  - Liver disease
- Endocrine disorders
  - Anovulatory bleeding
  - Thyroid disease
  - Adrenal disorders
  - Hyperprolactinemia
  - Polycystic ovary syndrome
  - Ovarian failure
- Ovarian problems
  - Cyst
  - Tumor
- Endometriosis
- Trauma
- Foreign body
- Systemic disease
  - Diabetes mellitus
  - Renal disease
  - Systemic lupus erythematosus
- Medications
  - Hormonal
  - Anticoagulants, platelet inhibitors
  - Androgens, spironolactone
  - Antipsychotics

Menstruation in Girls and Adolescents: Using the Menstrual Cycle as a Vital Sign – ACOG – Committee Opinion 2015

AUB: anamnesi, esame obiettivo e strumentale

- ✓ Informazioni sulla "storia mestruale" (menarca, R, Q, D);
- ✓ Escludere disturbi alimentari, stress o eccessiva attività sportiva;
- ✓ Pz virgo?
- ✓ Pz nata a termine/pretermine

- ✓ Costituzione, distribuzione del grasso corporeo e iperandogenismo;
- ✓ Facilità a sviluppare ecchimosi, ematomi;
- ✓ Sviluppo delle mammelle (eventuale galattorrea) e dei genitali esterni (stadi di Tanner);
- ✓ Palpazione addominale (escludere masse uterine/ovariche);

- ✓ Ecografia pelvica TA/TV (valutazione di eventuali malformazioni uterine)
- ✓ Esami di laboratorio.

AUB: indagini di laboratorio

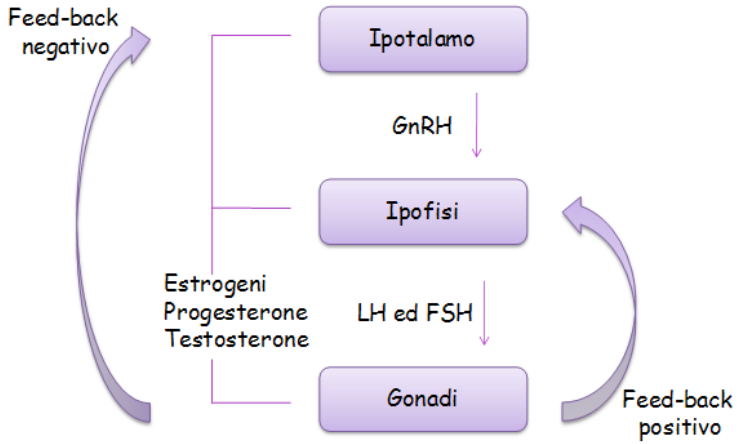
Laboratory Evaluation	Specific Laboratory Tests
Initial laboratory testing	• Complete blood count • Blood type and cross match • Pregnancy test
Initial laboratory evaluation for disorders of hemostasis	• Partial thromboplastin time • Prothrombin time • Activated partial thrombo-plastin time • Fibrinogen
Initial testing for von Willebrand disease*	• von Willebrand factor antigen† • Ristocetin cofactor assay† • Factor VIII†
Other laboratory tests to consider	• 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.

Management of Acute Abnormal Uterine Bleeding in Nonpregnant Reproductive-Aged Women – ACOG – Committee Opinion 2015

AUB-O



Causes of anovulatory genital tract bleeding in adolescents

Age-related	Medications
Immature hypothalamic-pituitary-ovarian axis at the onset of menarche	Oral contraceptives
Systemic illness and neoplasms	Progestins
Hypothyroidism and hyperthyroidism	Antipsychotic drugs
Chronic liver and renal disease	Corticosteroids
Hypercortisolism (Cushing syndrome)	Chemotherapeutic agents
Polycystic ovary syndrome	**Other**
Prolactinoma	Sudden weight loss
Empty sella syndrome	Stress
Pituitary infarction after postpartum hemorrhage (Sheehan syndrome)	Intense exercise
Adrenal and ovarian tumors	
Tumors infiltrating the hypothalamus	

La causa più frequente di AUB nelle adolescenti è imputabile all'immaturità dell'asse ipotalamo-ipofisi-ovaio.

AUB-O: classificazione

	Lieve	Moderato	Severo
Durata/Ritmo	> 7 gg o cicli <24 gg per ≥2 mesi	> 7 gg o cicli di 7-21 gg	”
↑ Flusso	↑	↑↑	↑↑↑
Hb	Normale o lievemente diminuita (10-12 g/dL)	≥ 10 g/dL	≤10 g/dL

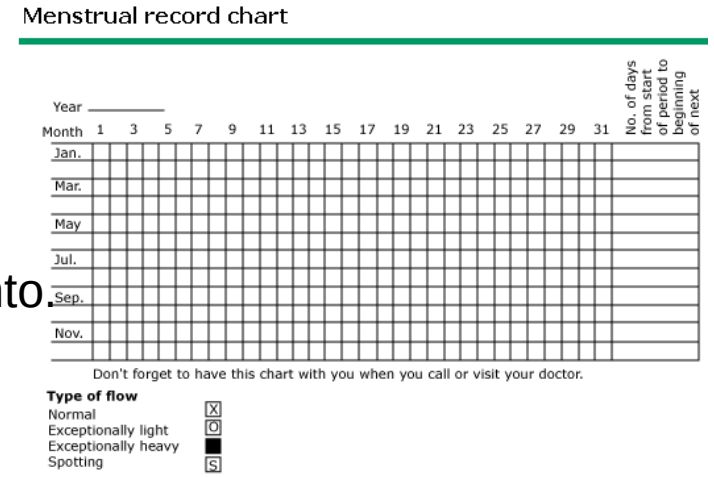
Adolescent menstrual disorders. Update. AU Mitan LA, Slap GB SO Med Clin North Am. 2000

AUB-O: management

- Mantenere la stabilità emodinamica;
- Ripristinare cicli mestruali normali;
- Prevenire recidive;
- Prevenire conseguenze a lungo termine.

Premesse

- Escludere altre diagnosi;
- Controllare lo stato di anemia sideropenica;
- Valutare l'effetto ormonale;
- Follow up della risposta della paziente al trattamento.



AUB-O lieve: management

	Lieve	Moderato	Severo
Durata/Ritmo	**> 7 gg o cicli <24 gg per ≥2 mesi**	> 7 gg o cicli di 7-21 gg	”
↑ Flusso	↑	↑↑	↑↑↑
Hb	**Normale o lievemente diminuita (10-12 g/dL)**	≥ 10 g/dL	≤10 g/dL

- Hb 10-12 g/dL: Watch and see / terapia ormonale + supplementazione di ferro;

- Hb > 12 g/dL: Watch and see;

Follow up

- Hb 10-12 g/dL: follow up a 3 mesi dall’episodio iniziale, per testare l’efficacia del trattamento;

- Hb > 12 g/dL: follow up a 3-6 mesi, per valutare la risoluzione del quadro o la necessità di impostare una terapia ormonale.

Adolescent menstrual disorders. Update. AU Mitan LA, Slap GB SO Med Clin North Am. 2000

AUB-O moderato: management

	Lieve	Moderato	Severo
Durata/Ritmo	> 7 gg o cicli <24 gg per ≥2 mesi	**> 7 gg o cicli di 7-21 gg**	”
↑ Flusso	↑	↑↑	↑↑↑
Hb	Normale o lievemente diminuita (10-12 g/dL)	**≥ 10 g/dL**	≤10 g/dL

2 situazioni:

- Sanguinamento in atto: terapia estroprogestinica;
- Assenza di sanguinamento in atto: monitoraggio fino a terapia estroprogestinica.

Follow up

- A 3 mesi, eventualmente incrementando la dose di estroprogestinici e, se necessario, prescrivendo acido tranexamico;
- A 1 anno, se quadro clinico stabile.

Adolescent menstrual disorders. Update. AU Mitan LA, Slap GB SO Med Clin North Am. 2000

AUB-O: terapia e limiti

THE COCHRANE COLLABORATION®

[Intervention Review]

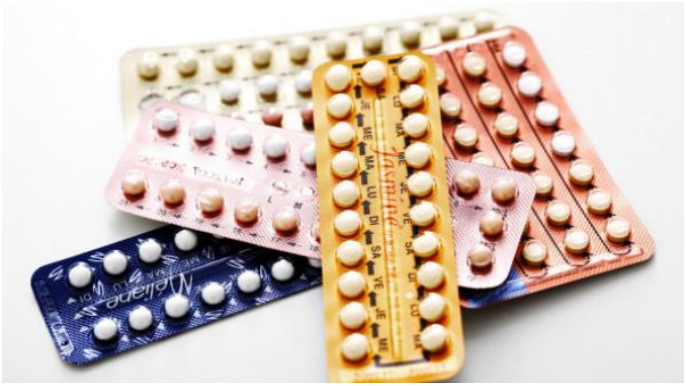
Progestogens versus oestrogens and progestogens for irregular uterine bleeding associated with anovulation

Cochrane Database Syst Rev. 2012

"There is a paucity of randomised studies relating to the use of progestogens and of oestrogens and progestogens in combination in the treatment of irregular bleeding associated with anovulation.
Further research is needed to establish the role of these treatments in the management of this common gynaecological problem."

Opzioni terapeutiche:

- Estrogeni equini coniugati EV;
- Estroprogestinici;
- Progestinici;
- Antifibrinolitici.



AUB-O: terapia

Drug	Source	Suggested Dose	Dose Schedule	Potential Contraindications and Precautions According to FDA Labeling*
Conjugated equine estrogren	DeVore GR, Owens O, Kase N. Use of intravenous Premarin in the treatment of dysfunctional uterine bleeding—a double-blind randomized control study. Obstet Gynecol 1982;59: 285–91.	25 mg IV	Every 4–6 hours for 24 hours	Contraindications include, but are not limited, to breast cancer, active or past venous thrombosis or arterial thromboembolic disease, and liver dysfunction or disease. The agent should be used with caution in patients with cardio-vascular or thromboembolic risk factors.
Combined oral contraceptives†	Munro MG, Mainor N, Basu R, Brisinger M, Barreda L. Oral medroxyprogesterone acetate and combination oral contraceptives for acute uterine bleeding: a randomized controlled trial. Obstet Gynecol 2006;108:924–9.	Monophasic combined oral contraceptive that contains 35 micrograms of ethinyl estradiol	Three times per day for 7 days	Contraindications include, but are not limited to, cigarette smoking (in women aged 35 years or older), hypertension, history of deep vein thrombosis or pulmonary embolism, known thromboembolic disorders, cerebrovascular disease, ischemic heart disease, migraine with aura, current or past breast cancer, severe liver disease, diabetes with vascular involvement, valvular heart disease with complications, and major surgery with prolonged immobilization.
Medroxypro-gesterone acetate‡	Munro MG, Mainor N, Basu R, Brisinger M, Barreda L. Oral medroxyprogesterone acetate and combination oral contracep-tives for acute uterine bleeding: a randomized controlled trial. Obstet Gynecol 2006;108:924–9.	20 mg orally	Three times per day for 7 days	Contraindications include, but are not limited to, active or past deep vein thrombosis or pulmonary embolism, active or recent arterial thromboembolic disease, current or past breast cancer, and impaired liver function or liver disease.
Tranexamic acid	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.	1.3 g orally§ or 10 mg/kg IV (maximum 600 mg/dose)	Three times per day for 5 days (every 8 hours)	Contraindications include, but are not limited to, acquired impaired color vision and current thrombotic or thromboembolic disease. The agent should be used with caution in patients with a history of thrombosis (because of uncertain thrombotic risks), and concomitant administration of combined oral contraceptives needs to be care-fully considered.

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AUB-O severo: management e terapia

	Lieve	Moderato	Severo
Durata/Ritmo	> 7 gg o cicli <24 gg per ≥2 mesi	> 7 gg o cicli di 7-21 gg	”
↑ Flusso	↑	↑↑	↑↑↑
Hb	Normale o lievemente diminuita (10-12 g/dL)	≥ 10 g/dL	**≤10 g/dL**

Indicazioni per l'ospedalizzazione:

- Instabilità emodinamica (ipotensione, tachicardia);
- Emoglobina < 7 g/dL o < 10 g/dL con PE attive in atto;
- Anemia sintomatica (astenia, letargia);
- Necessità di terapia EV o approccio chirurgico.

Approfondimenti diagnostici:

- Escludere disordini della coagulazione;
- Ecografia pelvica TA/TV.

Terapia

- Terapia ormonale estroprogestinica come approccio iniziale;
- Terapia emostatica nel caso in cui il sanguinamento non sia gestibile nelle prime 24-48 ore di terapia ormonale o in caso di alterazioni piastriniche;

Follow up

Controllo a breve termine, fino a valori di Hb > 10 g/dL.

Adolescent menstrual disorders. Update. AU Mitan LA, Slap GB SO Med Clin North Am. 2000

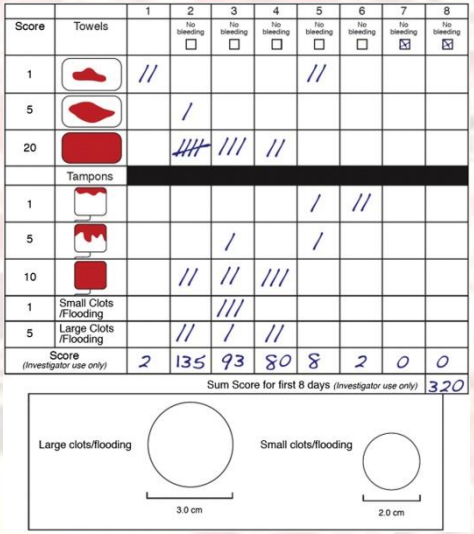
AUB-C: l'importanza della DD

• L'AUB è il sintomo più comune nelle adolescenti affette da disordini della coagulazione;

• Il 36%-44% delle adolescenti affette da AUB presenta malattia di Von Willebrand o alterazioni piastriniche;

Management

- Esami ematochimici specifici: emocromo completo con formula, PT, aPTT, vWF, fattore VIII;
- Gli esami ematochimici destinati allo studio ipocoagulativo dovrebbero precedere l'infusione di EC o di estrogeni;
- Importanza dell'anamnesi e della valutazione multidisciplinare;
- Strumenti pratici di quantificazione delle PE in sospette coagulopatie (PBAC score).



Bleeding Disorders in Adolescents – Andra H. James, MD,MPH - 2009 Elsevier Inc.

AUB-O: PCOS

Come fare diagnosi?

Criteri di Rotterdam:

1) Iperandrogenismo;
2) Irregolarità mestruale persistente (anovulazione);
3) Ovaie policistiche.

Diagnostica US:

- Presenza di 12 o più follicoli in una o entrambe le ovaie con diametro di 2-9 mm e/o incremento del volume ovarico (>10 ml)
- Approccio TV

LIMITE: non esistono criteri prestabiliti nelle adolescenti

2003 - Rotterdam Consensus Conference

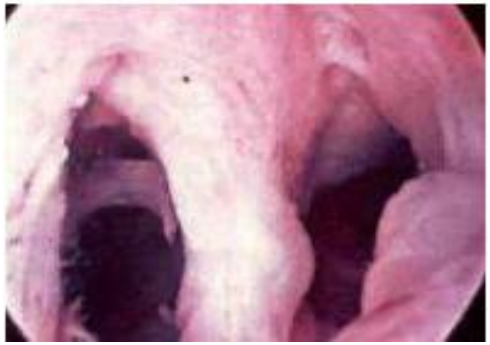
AUB: malformazioni dell'apparato genitale

- Anomalie dei genitali possono dare sanguinamenti anomali (spotting intermestruale-**IMB**);

- Malformazioni ostruttive possono associarsi a quadri di ematocolpo/ematometra e qualora parziali possono manifestarsi con sintomatologia algica e spotting periodico.

Setti vaginali:

- *longitudinali;*
- *trasversali;*



AUB: management a lungo termine

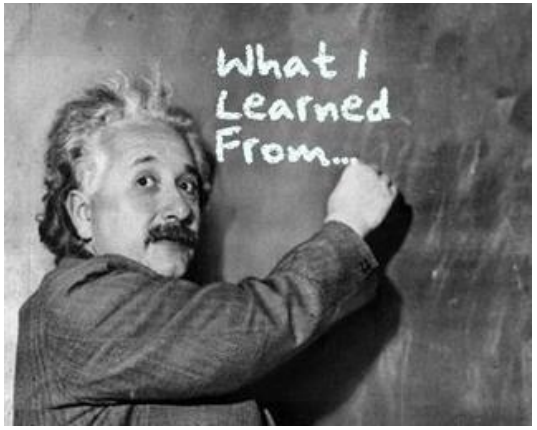
- Terapia di mantenimento dopo l'episodio acuto.

- Necessaria valutazione endocrinologica, se al termine della terapia ormonale non vi è una mestruazione entro i 3 mesi dalla terapia in acuto

Valutazione di: - FSH,
- LH,
- PRL,
- DHEA-S,
- 17-OH-progesterone,
- testosterone,
- TSH,
- insulino-resistenza

DD fra:
- immaturità asse H-P-O
- PCOS
- Iperprolattinemia
- Ipo-ipertiroidismo
- sindrome metabolica.

AUB: conclusioni



- Individuare quanto prima la causa dell'AUB;
- Escludere eziologia non ginecologica/ostetrica;
- Importanza dell'approccio multidisciplinare;
- Terapia "su misura"→ compliance della Pz;
- Evitare conseguenze a lungo termine.