

Normal Menstrual bleeding

- Triggered by progesterone withdrawal
- Endometrial necrosis and sloughing due to arteriolar vasoconstriction, spasm and necrosis
- PgF2 alpha mediated increase in endometrial contraction,
- Cessation of menses is a result of prolonged vasoconstriction, tissue collapse, vascular stasis and thrombin production as well as follicular recruitment and production of estradiol

Definitions

Normal:

Mean interval is 28 days $\pm$ 7 days.

Mean duration is 4 days.

More than 7 days is abnormal.

Average blood loss with menstruation is 35-50cc.

95% of women lose <60cc.

AUB

Abnormal uterine bleeding (AUB):
fairly broad term referring to bleeding
that occurs outside of normal cyclic
menstruation

AUB is a nonspecific term that describes a broad range of clinical presentations. It is best defined as bleeding that is excessive or occurs outside of normal cyclic menstruation.

There is an inconsistency in the nomenclature used to describe AUB, and does not provide necessary information on etiology of bleeding, coexisting uterine pathology, or underlying systemic diseases

CLINICAL CONTEXT

The terminology and definitions for AUB in nongravid women of reproductive age have been inconsistent, as reported by Woolcock and colleagues in the December 2008 issue of *Fertility and Sterility*. FIGO developed a system to classify AUB through a modified RAND/UCLA Delphi process.

This FIGO report describes the recommended classification system and terminology for causes of AUB in nongravid women of reproductive age.

La FIGO ha individuato 9 categorie di AUB, raggruppandole sotto l'acronimo **PALM-COEIN** (valido aiuto mnemonico per il [ginecologo](#) che deve porre diagnosi):

AUB-**P** : Polipi, la cui diagnosi può essere posta mediante ecografia transvaginale, sonoisterografia, isteroscopia;

AUB-**A** : Adenomiosi, la cui diagnosi è di tipo istologico, ma facilmente identificabile anche attraverso ecografia o isteroscopia;

AUB-**L** : Leiomiomi o fibromi, che possono essere unici o multipli, sottosierosi, sottomucosi o intramurali, identificabili anche questi attraverso ecografia, sonoisterografia o isteroscopia;

AUB-**M** : Malignità, comprendendo iperplasia con atipie cellulari e carcinoma endometriale, la cui diagnosi è essenzialmente istologica;

AUB-**C** : Coagulopatie, la cui diagnosi viene posta di solito in [età](#) adolescenziale (spesso Malattia di von Willebrand);

AUB-**O** : [Ovulazione](#) alterata, non potendosi prevedere la lunghezza e durata del ciclo;

AUB-**E** : Endometriale, dovuta ad anomala sintesi di prostaglandine o a fattori infettivi;

AUB-**I** : Iatrogena, la cui causa è legata all'assunzione di farmaci anticoagulanti oppure ormoni;

AUB-**N** : Non classificata, dovuta a malformazioni arterovenose o ipertrofia miometriale.

AUB (abnormal uterine bleeding)

- ✓ Definiti come anomali –disfunzionali se prolungati, frequenti o eccessivi, in assenza di patologia organica
- ✓ Elevata prevalenza nel mondo ¹
- ✓ 9-14% di donne hanno con flussi mestruali abbondanti ¹
- ✓ Problema spesso” poco percepito ” dalle donne italiane:
Il 25% di chi ha flussi superiori alla norma non ne ha mai parlato con il proprio ginecologo
- ✓ Anemizzazione
- ✓ Possono avere un impatto significativo sulla QoL¹
 - Diminuzione dell'efficienza lavorativa
 - Disagio emozionale
 - Interventi chirurgici

¹Heavy Menstrual Bleeding; NICE Clinical Guideline, January 2007

Fraser ,2009

Definitions

Menorrhagia:

Prolonged > 7 days or > 80 cc
occurring at regular intervals.

Synonymous with hypermenorrhea

Menorrhagia occurs in 9-14% of healthy women.

Definitions

Metrorrhagia:

Uterine bleeding occurring at
irregular but frequent
intervals.

Definitions

Menometrorrhagia:

Prolonged uterine bleeding
occurring at irregular
intervals.

Definitions

Oligomenorrhea:

Infrequent uterine bleeding
varying between 35 days and
6 months.

Definitions

Amenorrhea:

No menses for 6 months.

Office Diagnosis and Management of Abnormal Uterine Bleeding

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TABLE 1. Definition of Abnormal Uterine Bleeding

Intermenstrual bleeding	Bleeding between menstrual cycles
Metrorrhagia	Irregular bleeding
Menorrhagia	Excessive bleeding at regular intervals
Polymenorrhea	Menstrual cycle interval < 21 d
Oligomenorrhea	Menstrual cycle interval > 35 d
Menometrorrhagia	Excessive bleeding at irregular interval
Postmenopausal bleeding	Genital tract bleeding occurring > 12 months after the last menstrual period

www.clinicalobgyn.com

Etiologies

- Organic
 - Systemic
 - Reproductive tract disease
 - Iatrogenic
- Dysfunctional
 - Ovulatory
 - Anovulatory

TABLE 2. Differential Diagnosis of Abnormal Uterine Bleeding According to Age Groups

<u>Neonate</u>	<u>Reproductive Year</u>
Estrogen withdrawal	Anovulation
<u>Premenarchal</u>	Pregnancy
Foreign body	Cancer
Trauma, sexual abuse	Polyps, fibroid, adenomyosis
Infection	Infection
Urethral prolapse	Endocrine dysfunction (PCOS, thyroid, pituitary adenoma)
Ovarian and vaginal tumor	Bleeding diathesis
Precocious puberty	Medication-related (OCP, antipsychotic)
<u>Early postmenarchal</u>	<u>Perimenopausal</u>
Anovulation	Anovulation
Bleeding diathesis	Polyps, fibroid, adenomyosis
Stress	Cancer
Pregnancy	<u>Menopause</u>
Infection	Atrophy
PCOS	Cancer
	Estrogen replacement therapy

PCOS indicates polycystic ovarian syndrome.

Systemic Etiologies

- Coagulation defects, Leukemia , ITP

10% to 47% of adolescents with heavy menstrual bleeding may have an underlying bleeding disorder. Von Willebrand disease and platelet dysfunction account for the most common hematologic disorders in this age group

- Thyroid dysfunction

Chronic medical problems such as disorders of liver, kidney, thyroid or adrenal

Etiologies

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 - Anovulatory

Reproductive Tract Causes

- Gestational events
- Malignancies
- Benign
 - Atrophy
 - Leiomyoma
 - Polyps
 - Cervical lesions
 - Foreign body
 - Infections

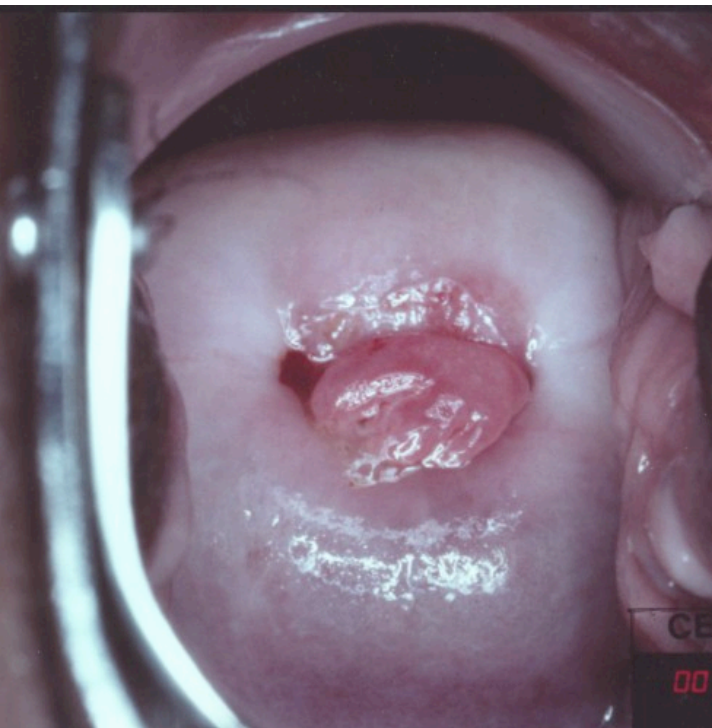
Reproductive Tract Causes of Benign Origin

- Atrophy (Post-menopausal)
- Leiomyoma
- Polyps
- Cervical lesions
- Foreign body (Pre-menarchal)
- Infection

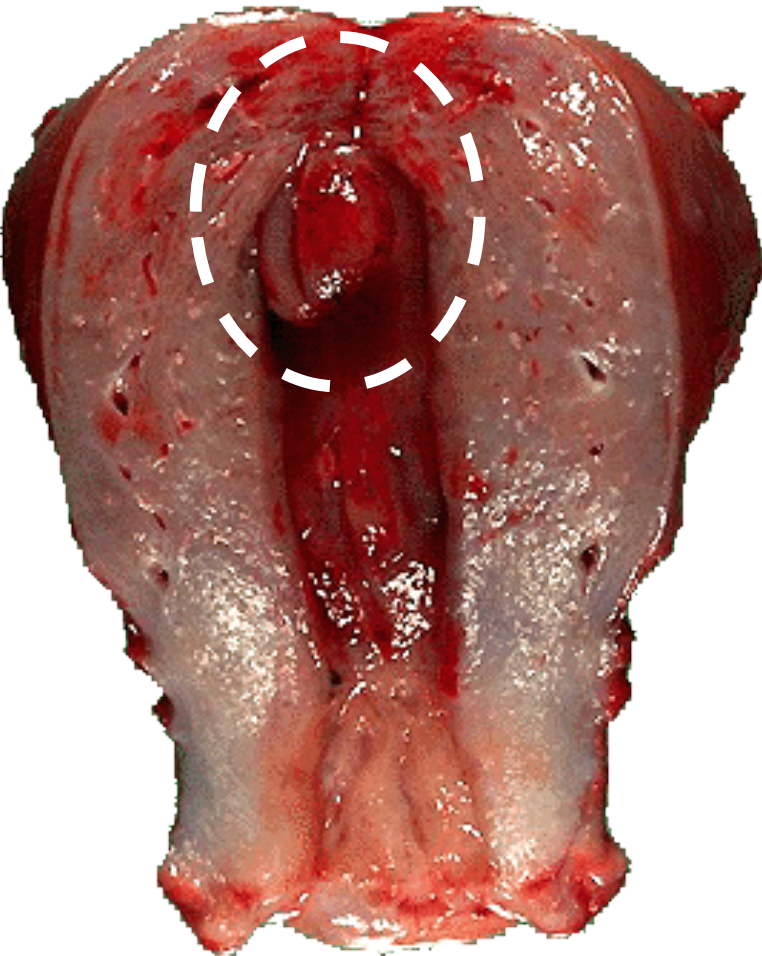


Polipi cervicali

- Singoli o multipli
- Sintomi: perdite ematiche da frizione-traumatismo fragilità vascolare
- Diagnosi: speculum
- Degenerazione maligna possibile ma estremamente rara
- Terapia: rimozione (dilatazione e raschiamento)



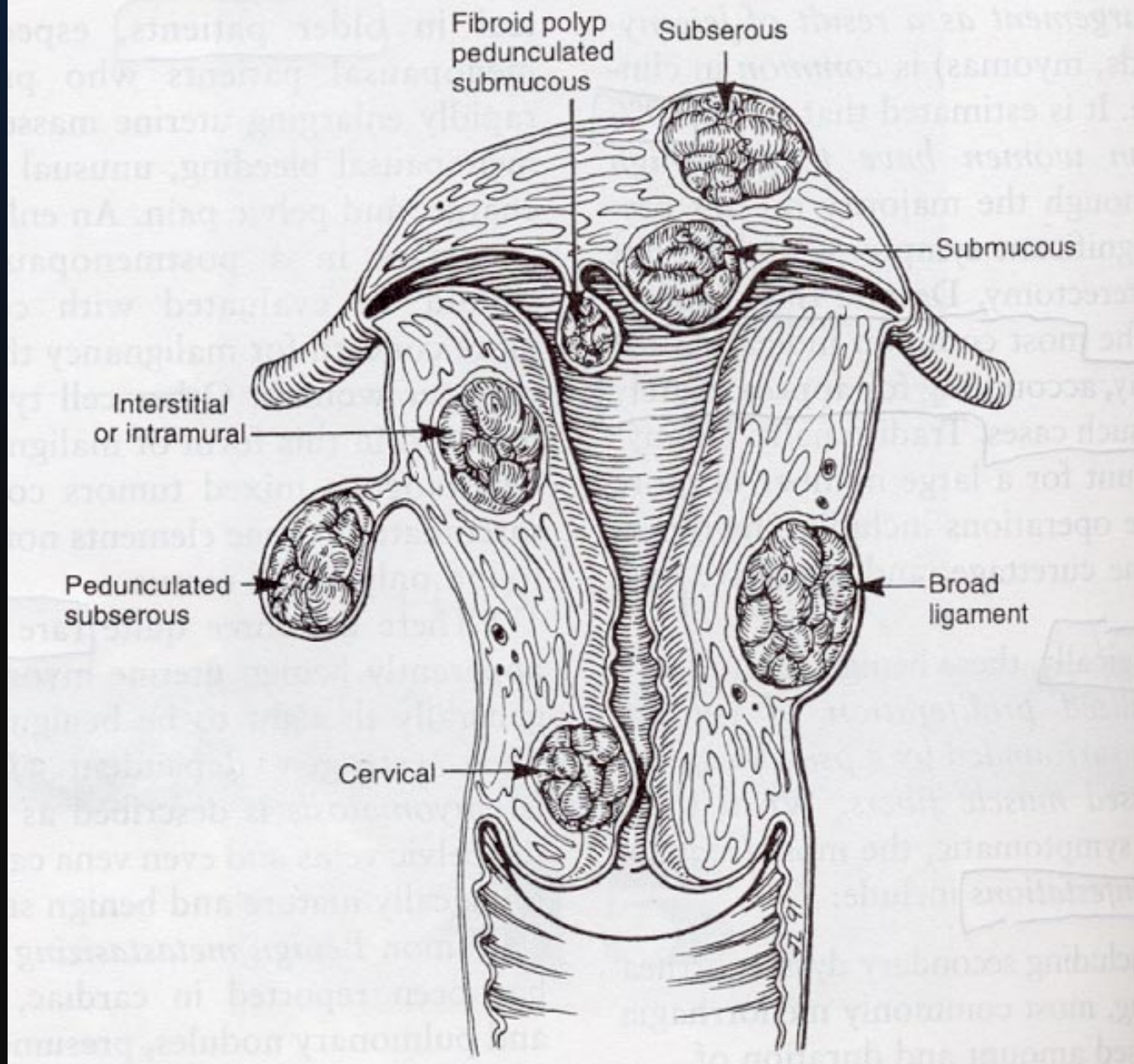
Tumori del corpo dell' utero: polipo endometriale



- Singoli o multipli
- Sintomi: perdite ematiche (fragilità vascolare ed erosione endometriale secondaria alla frizione della massa che protrude)
- Diagnosi: ecografia/ isteroscopia
- Degenerazione maligna possibile ma rara
- Terapia: rimozione (se sintomatici) con isteroscopia operativa

Fibroids (Leiomyomata)

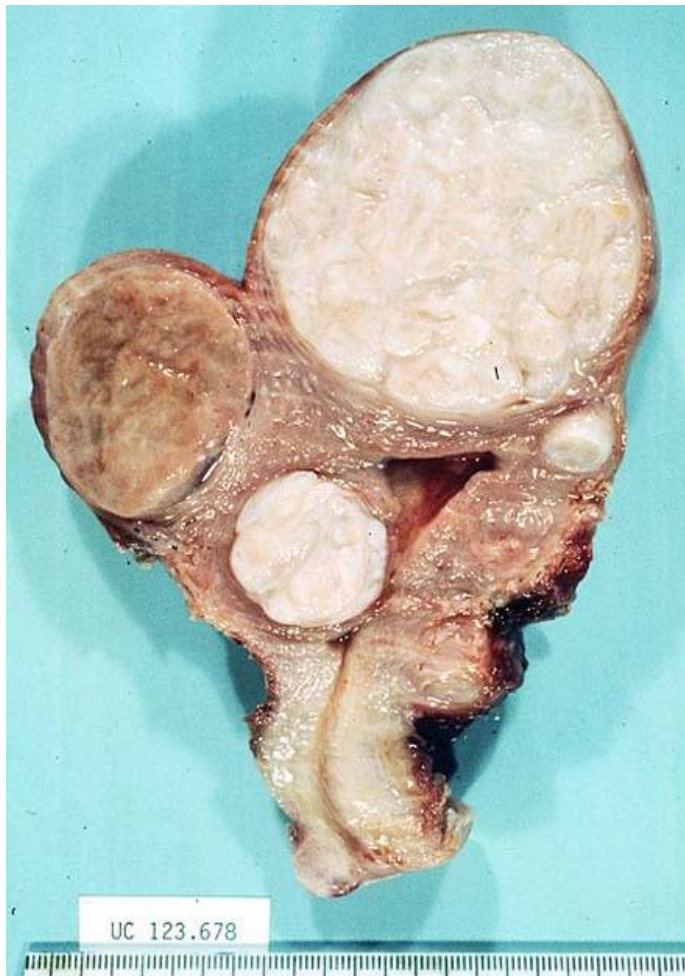
- Benign tumour
- Proliferation of smooth muscle with pseudocapsule of compressed muscle fibres
- 30% of reproductive age women
- Most common indication for hysterectomy (30%)



45.1. Common types of uterine fibroids.

The precise mechanism underlying bleeding in leiomyoma remains elusive.

The fragile abnormal angiogenesis with large-caliber vessels present in stretched and thin endometrium over submucosal fibroids can be a cause of bleeding and denuded endometrium preventing adequate hemostasis



60% of women with PMB* will
be found to have atrophy.

Karlsson, *et al.*, 1995

*post-menopausal bleeding

Reproductive Tract Causes

- Malignancies
 - Endometrial
 - Ovarian
 - Cervical (stadio avanzato)

In Italia l'incidenza dell'adenocarcinoma dell'endometrio è del 5-6% dei tumori femminili con circa 4.000 nuovi casi/anno.

-Pur essendo una malattia della postmenopausa 75%, il 25% dei casi si verifica nelle donne in età premenopausale, e il 2% in donne con meno di 40 anni .

Incidence of Endometrial Cancer in Premenopausal Women

2.3/100,000 in 30-34 yr old

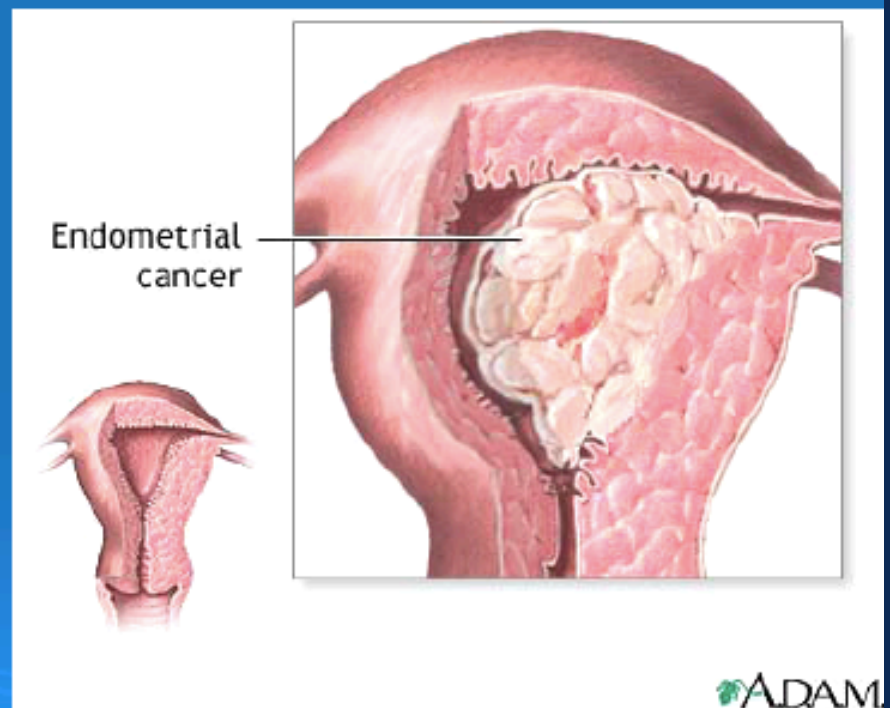
6.1/100,000 in 35-39 yr old

36/100,000 in 40-49 yr old

ACOG Practice Bulletin #14, 2000

Post menopausal bleeding and endometrial cancer

- Most common gyn cancer (>40,000 cases annually)
- Postmenopausal vaginal bleeding the presenting sign in >90% of cases
- Most PMB is atrophic but:
- 1-14% of women with PMB will have endometrial cancer



FATTORI DI RISCHIO

Molti dei fattori di rischio sono associati ad una prolungata esposizione dell'endometrio ad estrogeni circolanti in assenza di un effetto differenziante del progesterone.

- **Obesità (rischio relativo 1,9-11)**
- **Menarca precoce**
- **Menopausa tardiva (r.r 1,6-2,4)**
- **Bassa parità**
- **Sindrome dell'ovaio policistico**
- **Tumori secernenti estrogeni**
- **Terapia estrogenica non contrapposta (r.r 1,6-12)**
- **Terapia con Tamoxifene**
(aumenta il rischio da 2 a 7 volte legato alla durata di assunzione)

IPERPLASIA ENDOMETRIALE

FATTORI DI RISCHIO



IPERESTROGENISMO



IPERPLASIA ENDOMETRIALE

Semplice

Complessa

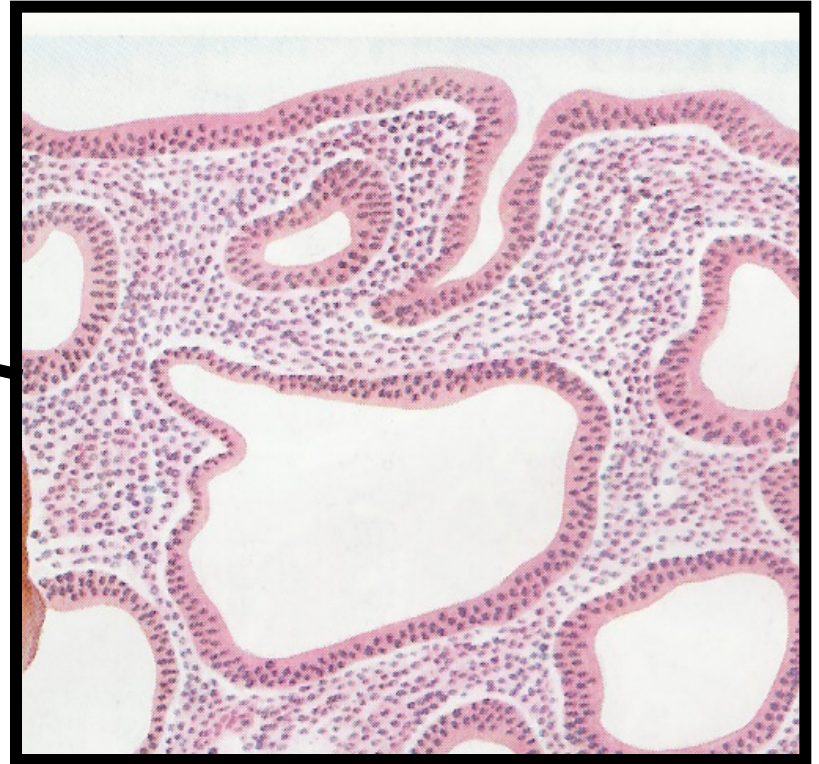
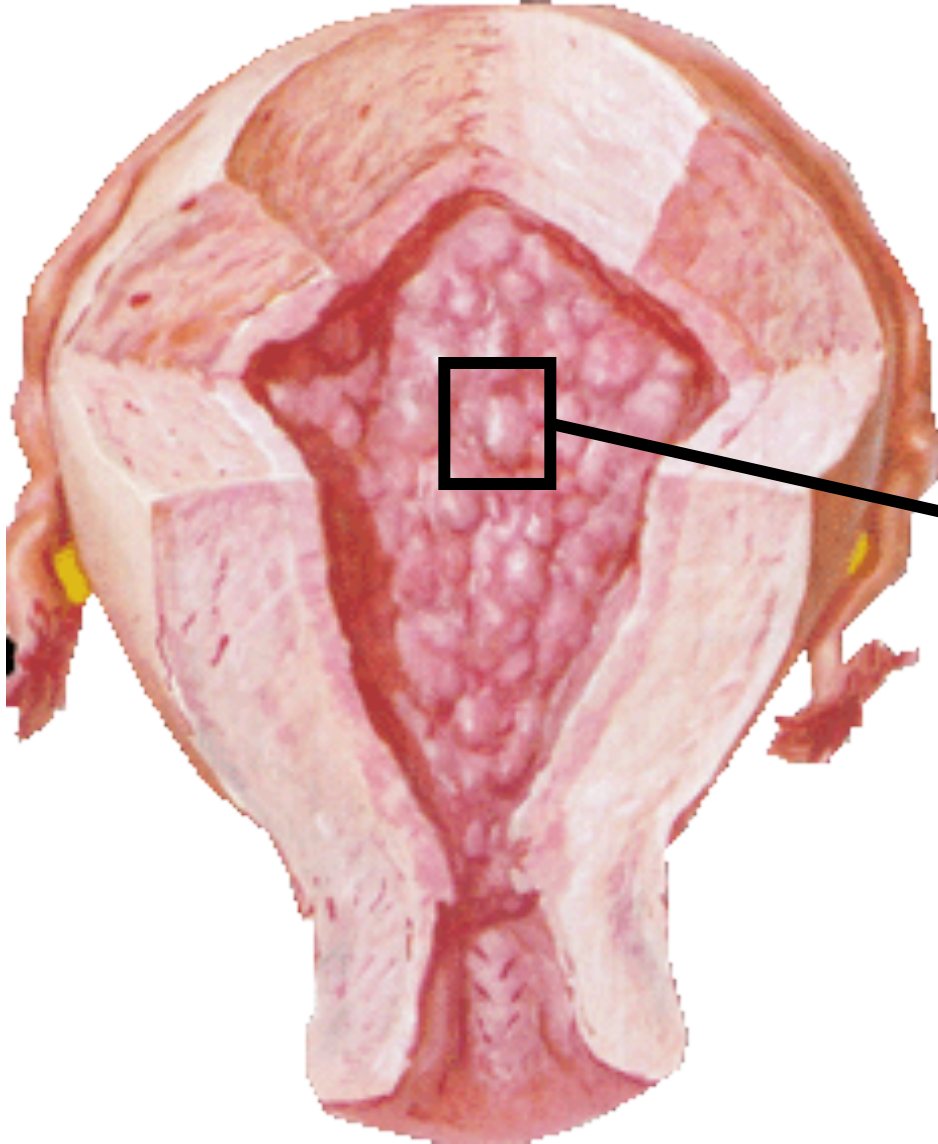
Atipica

20-30%

ADENOCARCINOMA ENDOMETRIALE



Iperplasia dell' endometrio



Etiologies

- Organic
 - Systemic
 - Reproductive tract disease
- Iatrogenic
- Dysfunctional
 - Ovulatory
 - Anovulatory

Iatrogenic Causes of AUB

- Intra-uterine device
- Hormones
- Psychotropic drugs

Etiologies

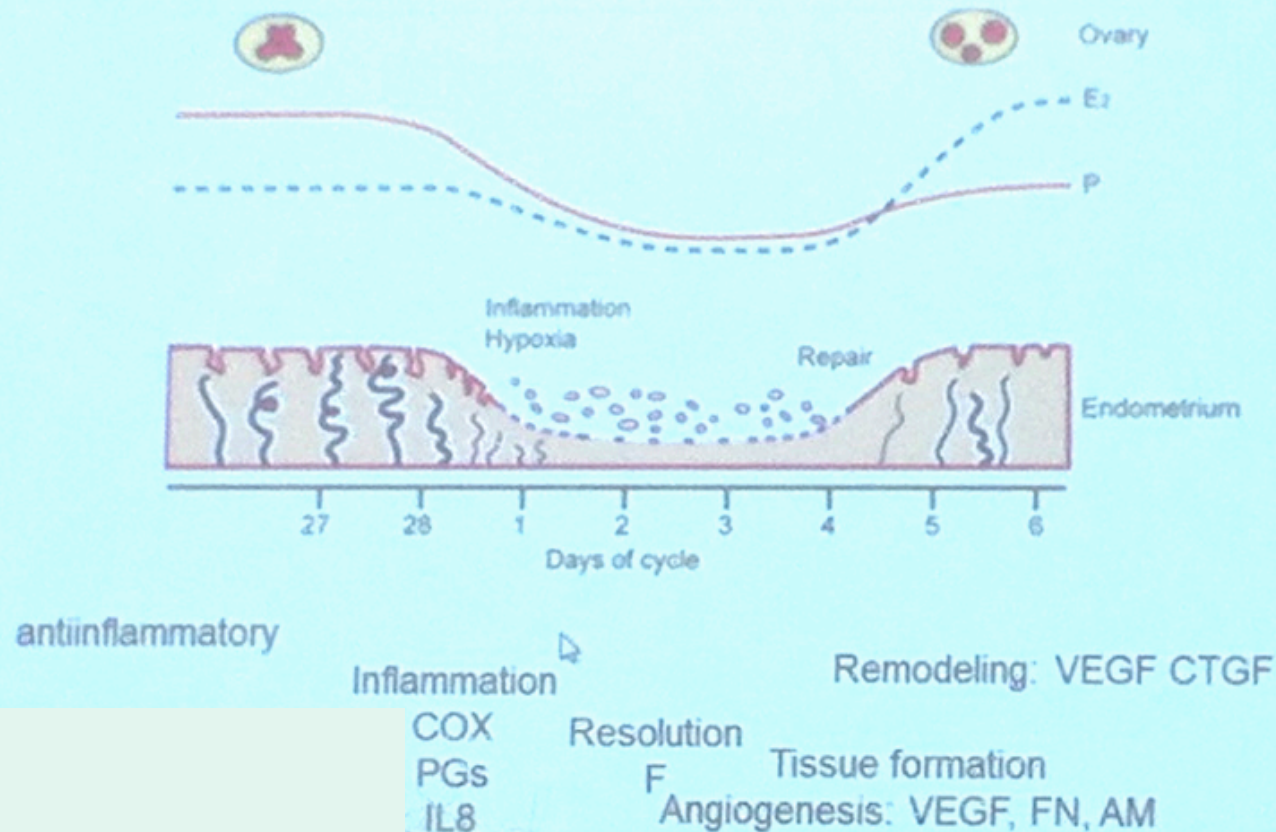
- Organic
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DUB

(dysfunctional uterine bleeding)

Abnormal uterine bleeding for which an organic etiology has been excluded. It is either ovulatory or anovulatory in origin.

Maybin & Critchley
 Annals NY Acad Sciences 1221: 88-97 2011
 Seminars in Reproductive Medicine 29: 400-409, 2011



Prog



(PG)F2a

(costrizione arterioli spirali –ipossia)

Reazione infiammatoria e degradazione tissutale

Riparazione

The majority of dysfunctional AUB in the premenopausal woman is a result of anovulation.

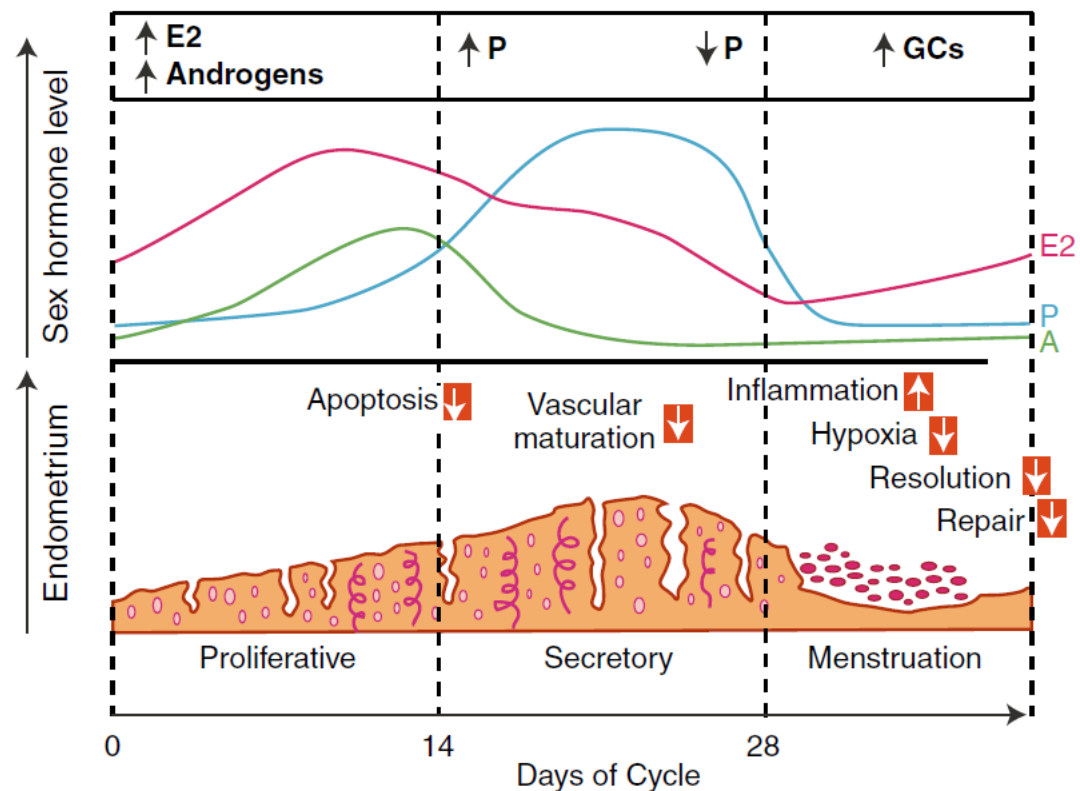
Comprehensive Gynecology, 4th edition

With anovulation a corpus luteum is NOT produced and the ovary thereby fails to secrete progesterone.

However, estrogen production continues, resulting in endometrial proliferation and subsequent hyperplasia and AUB .

Since vasoconstriction is promoted by $\text{PGF2}\alpha$, which is less abundant due to the decrease in progesterone, vasodilation results thereby promoting AUB.

Fig. 1 Steroid hormone levels across the human menstrual cycle and their functional impact on endometrial tissue. Red boxes show predicted abnormalities in women with heavy menstrual bleeding. *P* progesterone, *E2* estradiol, *A* androgens, *GC* glucocorticoids



MMP metalloproteinasi della matrice (inibite da Prog) prodotte dalle cell stromali scindono componenti della matrice extracell dello strato funzionale

AUB of endometrial origin

- some 400 menstrual cycle over the reproductive life
- repeated cycles of shedding and repair
- postmenstrual resolution of the inflammatory events associated with menstruation and endometrial repair remain to be fully determined
- healing of endometrium post menses is “scarless”

It is highly likely that unrestrained local inflammatory events and/or deficient repair process within the endometrium contribute to the experience of HMB (heavy menstrual bleeding)

To determine if DUB is ovulatory or anovulatory....

- History
- Daily basal body temperature
- Luteal phase progesterone
- Luteal phase EMB (endometrial biopsy)

AUB: Evaluation and Work-up

First of all : pregnancy and
malignancy must be ruled out.

Evaluation of Abnormal Uterine Bleeding

- History: frequency, duration volume and associated symptoms, onset of bleeding, family history, general health history, medication exposure
- Physical examination: basic physical for signs of systemic disease, body habitus pap smear, bimanual exam assessing uterine size contour, tenderness

Evaluation of AUB

- Laboratory:
 - pregnancy test
 - cervical cytology
 - cultures of the cervix
 - CBC
- Evaluation of the endometrium:
 - Endometrial biopsy
 - TVUS
 - SIS
 - Hysteroscopy

Transvaginal Ultrasonography (TVS)

- Inexpensive, noninvasive, and convenient
- Indirect visualization of the endometrial cavity, myometrium, and adnexa
- Measurement of endometrial thickness (<5 mm vs. >5 mm) high NPV to exclude endometrial carcinoma in postmenopausal
- Useful with insufficient EMB or as first line evaluation with PMB
- May be used to increase index of suspicion for endometrial atrophy, hyperplasia, cancer, leiomyomas, and polyps but low specificity

2. Indicazioni all'esame ecografico ginecologico

L'imaging ecografico ginecologico è una indagine strumentale non invasiva utile:

- 2.1 Nel percorso diagnostico delle neoformazioni sospettate su base anamnestica od obiettiva a carico dei genitali interni (Evidenza II-a. **Livello di raccomandazione A**).
- 2.2 Nel percorso diagnostico delle patologie disfunzionali e infettive che interessano o possono interessare i genitali interni (Evidenza II-b. Livello di raccomandazione B).
- 2.3 Nella diagnosi differenziale con altre patologie addomino pelviche in condizioni di urgenza (appendicopatie, diverticoliti, **malattie infiammatorie enteriche** (Evidenza III. Livello di raccomandazione C).
- 2.4 Nel percorso diagnostico di pazienti in peri- e post-menopausa con perdite ematiche atipiche, concorrendo a determinare i caratteri macroscopici dell'endometrio e della cavità uterina (Evidenza II-a. Livello di raccomandazione B).
- 2.5 Nella sorveglianza dell'ovaio e dell'endometrio in soggetti ad alto rischio di patologia neoplastica ovarica od endometriale (familiarità per carcinoma ovarico o sindromi familiari per tumori epiteliali, farmaci) (Evidenza II-a. Livello di raccomandazione B).
- 2.6 Nel monitoraggio dell'ovulazione spontanea e farmacologicamente indotta (Evidenza II-b).
- 2.7 Nel monitoraggio di terapie mediche e nel controllo di esiti chirurgici (Evidenza IV. Livello di raccomandazione C).



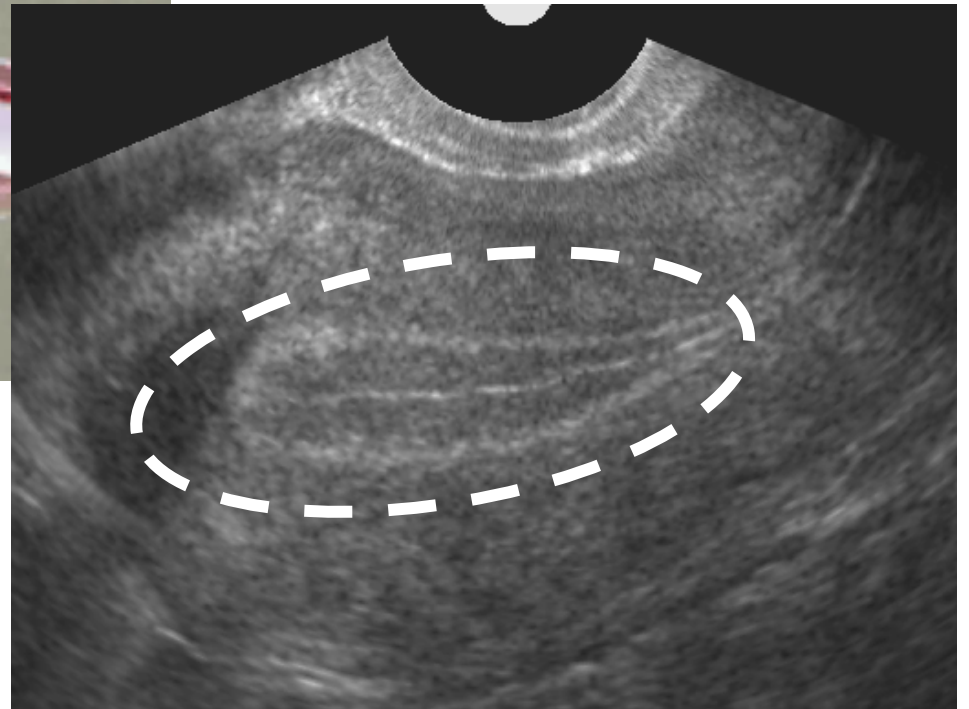
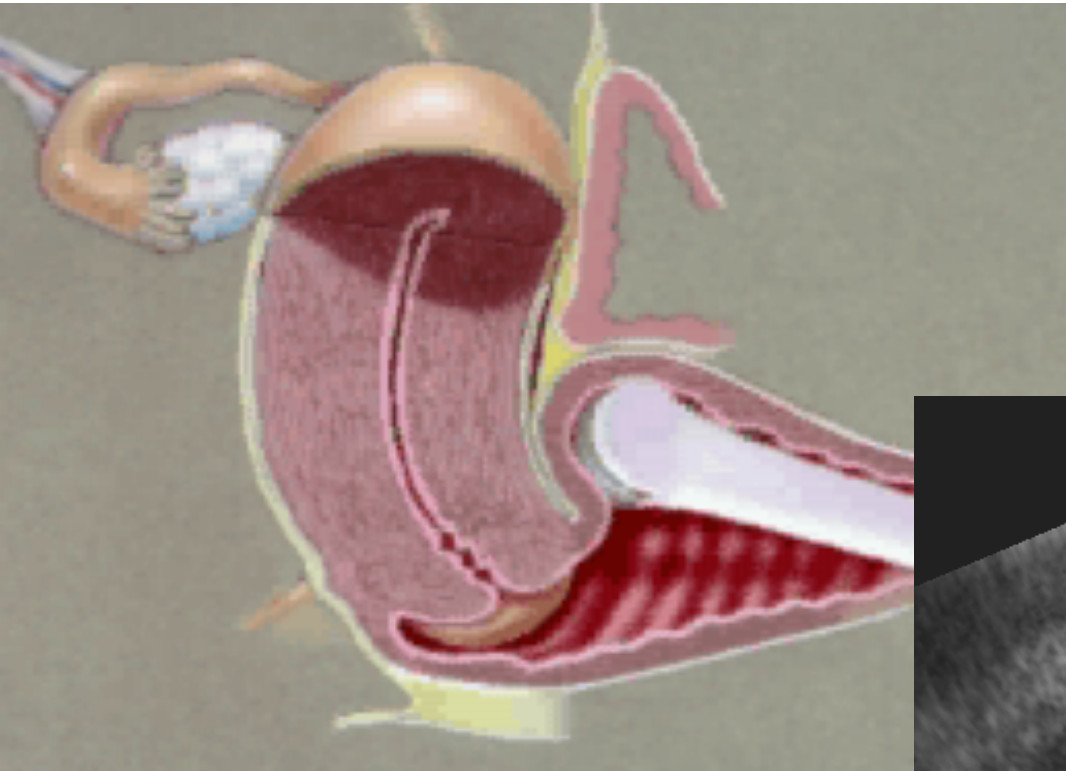
4.2 Condizioni a rischio oncologico

- 4.2.1 L'impiego dell'ecografia endovaginale per definire un rischio oncologico ovarico o endometriale è riconosciuto attualmente solo per quanto riguarda lo studio dell'endometrio in pazienti post-menopausali con perdite ematiche atipiche, e per pazienti ad alto rischio di carcinoma dell'ovaio. Spessore ≤ 4 mm è considerato adeguato a differenziare una condizione di ipo-atrofia rispetto a condizioni a rischio oncologico. Uno spessore ≤ 5 mm diminuisce la sensibilità del test a scapito della specificità, e il suo impiego può essere considerato in questa luce (Evidenza II-a).
- 4.2.2 In pazienti in terapia ormonale sostitutiva l'esame ecografico deve essere eseguito tenendo conto dell'eventuale fase del ciclo terapeutico al fine di eseguire l'esame nel periodo in cui si presume l'endometrio abbia lo spessore inferiore (Evidenza III).

www.sieog.it, 2010

According to a 2009 American College of Obstetricians and Gynecologists Committee Opinion¹⁴ a thin distinct endometrial echo on TVS ≤ 4 mm has a risk of malignancy of 1 in 917, and therefore endometrial biopsy is not required

Ecografia endovaginale per la visualizzazione dell' endometrio

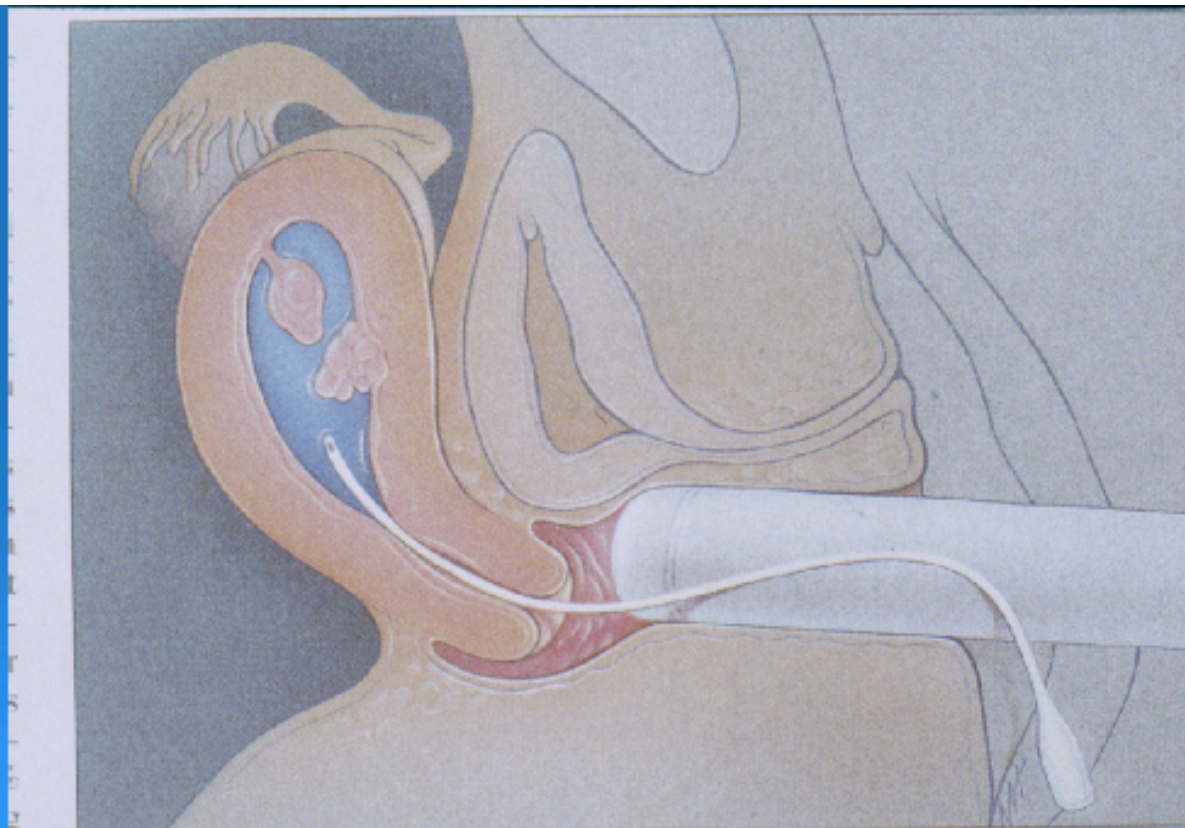


Saline Infusion Sonography (SIS)

- Very useful for evaluation of AUB in pre-, peri-, and postmenopausal women
- May be superior to TVS alone (94.1% vs. 23.5% for detection of focal intrauterine pathology)
- SIS + biopsy: 96.2% sensitivity and 98% specificity
- Able to determine penetration depth of uterine fibroids
- Disadvantage: small irregularities may be misinterpreted as polyps

1. Finalità dell' esame sonoisterografico

- 1.1 Valutare la morfologia della cavità uterina.
- 1.2 Identificare e/o escludere patologie uterine endocavitarie.
- 1.3 Fornire indicazioni al chirurgo sul tipo di approccio chirurgico da seguire e valutarne i risultati conseguiti.



Endometrial Biopsy

- Safe, relatively simple procedure useful in perimenopausal or high risk women to exclude cancer of the uterus or precancer conditions
- Not sensitive for detecting structural abnormalities (eg, polyps or fibroids)
- Indicated for women over 35 or younger with associated risk factors
- Office-based techniques (gold standard replacing D&C)

EMB

- Sensitivity 90-95%
- Easy to perform
- Numerous sampling devices available



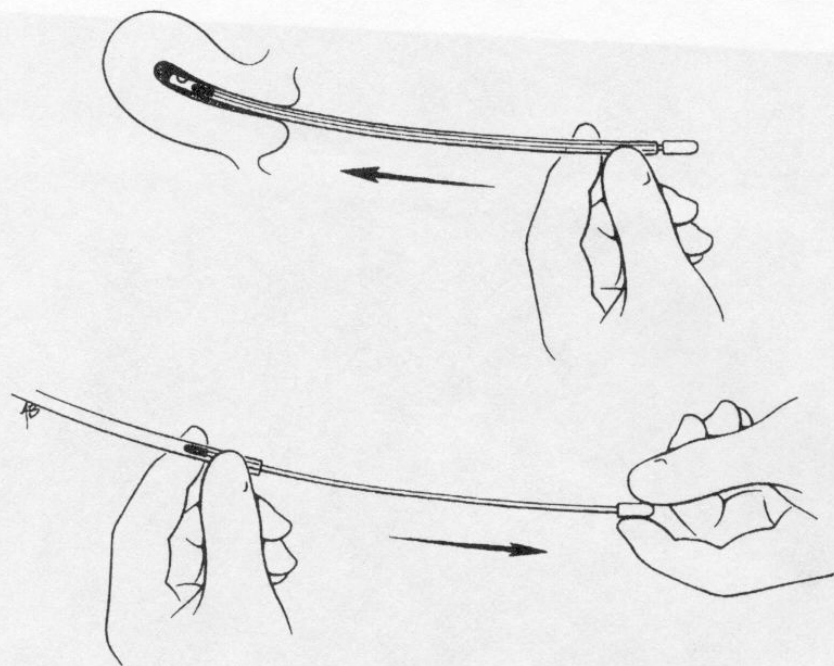


FIGURE 33.6. Endometrial biopsy using Pipelle. Hollow tube held in uterine cavity as stylet is withdrawn generating aspiration.

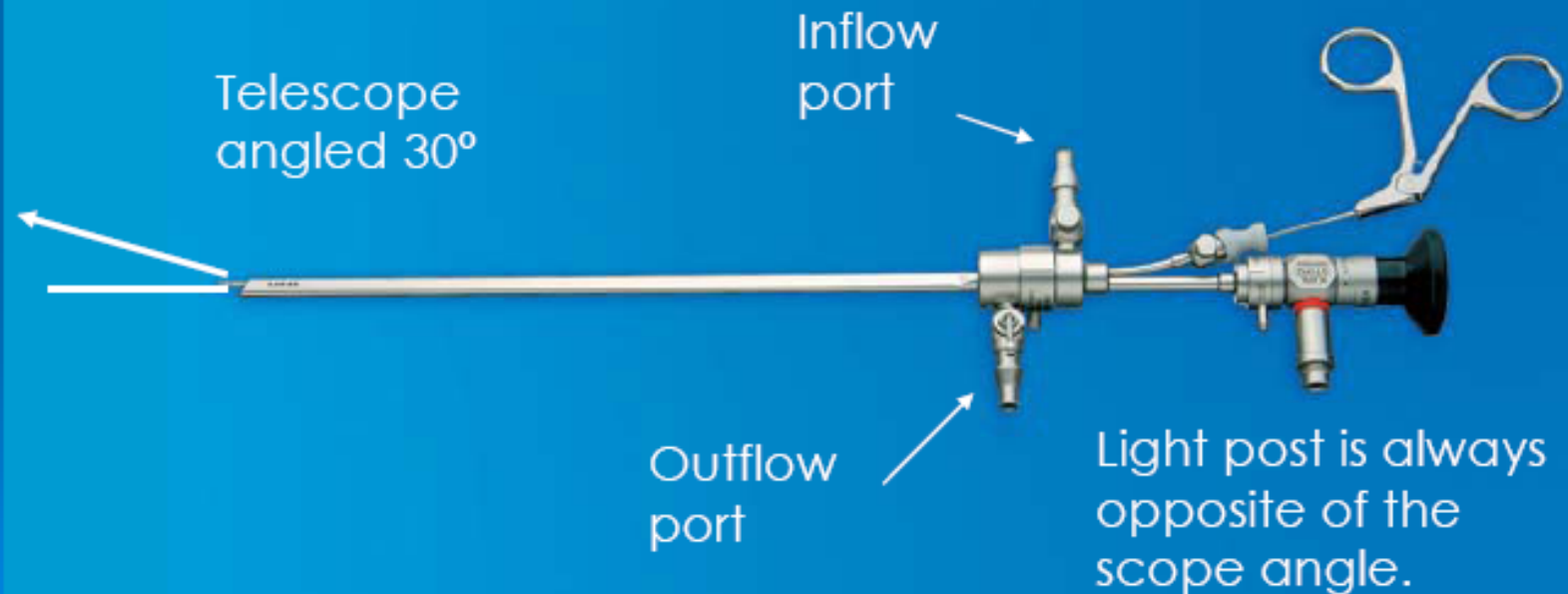


Possible Endometrial Biopsy Findings

- Proliferative, secretory, benign, or atrophic endometrium
- Inactive endometrium
- Tissue insufficient for analysis
- No endometrial tissue seen
- Simple or complex (adenomatous) hyperplasia without atypia
- Simple or complex (adenomatous) hyperplasia with atypia
- Endometrial adenocarcinoma

Diagnostic Techniques in AUB

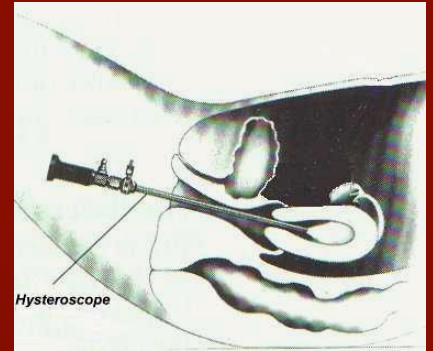
Hysteroscopy



Hysteroscopy

- Hysteroscopy + biopsy = “gold standard”
- Most are performed to evaluate AUB
- Diagnostic hysteroscopy easily performed in the office setting—although it requires skill
- Particularly useful in the diagnosis of intrauterine lesions in women of reproductive age with ovulatory AUB
- Complications (<1%) may include uterine perforation, infections, excessive bleeding, and those related to distending medium

CHE COS'È L'ISTEROSCOPIA?



L'isteroscopia è una procedura che utilizza uno strumento endoscopico che trasmette luce, che viene inserito attraverso la cervice nella cavità uterina distesa da un mezzo di distensione liquido o gassoso.

L'isteroscopia permette la visualizzazione diretta del canale cervicale e della morfologia della cavità uterina, con lo scopo di valutare (Isteroscopia diagnostica) e, quando possibile, trattare (Isteroscopia operativa) le patologie endocavitarie eventualmente riscontrate.

L'isteroscopia è oggi l'indagine **gold standard** nella pratica clinica ginecologica, per numerose patologie organiche e disfunzionali e nello studio dell'infertilità.

Summary

- AUB is a significant gynecologic health problem
- Anovulatory uterine bleeding is a diagnosis of exclusion
- Uterine pathology can be evaluated by: biopsy, TVS, hysteroscopy, SIS, and MRI
- Medical therapy is generally preferred
- Surgical treatments for AUB include removal of the anatomic lesion, hysterectomy, hysteroscopic endometrial ablation/resection, free fluid ablation, and nonhysteroscopic endometrial ablation

Terapie di uso corrente per AUB/ flussi abbondanti

Non-ormonali	Ormonali	Chirurgiche
Acido tranexamico	IUD LNG	Ablazione endometriale
FANS	COC	Resezione endometriale
	Progestinici	Isterectomia
	Terapia ormonale altra	

Medical Treatment of AUB in the Reproductive years

- Iron
- Antifibrinolytics
- Cyclooxygenase inhibitors
- Progestins
- Estrogens + progestins (OCs)
- Parenteral estrogens (CEEs)
- GnRH agonists and antagonists
- Antiprogestational agents

Surgical Treatment of AUB

- Hysterectomy
- Hysteroscopic endometrial ablation
- Nonhysteroscopic endometrial ablation

Endometrial ablation: 1° or 2° generation?

First generation

- Hysteroscopic vision
- Energy
 - monopolar
 - bipolar
- General or locoregional anesthesia

Second generation

- Blind technique
- Several energy
- Without general anesthesia

