Abnormal Uterine Bleeding

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Disclosures

- I have no disclosures.

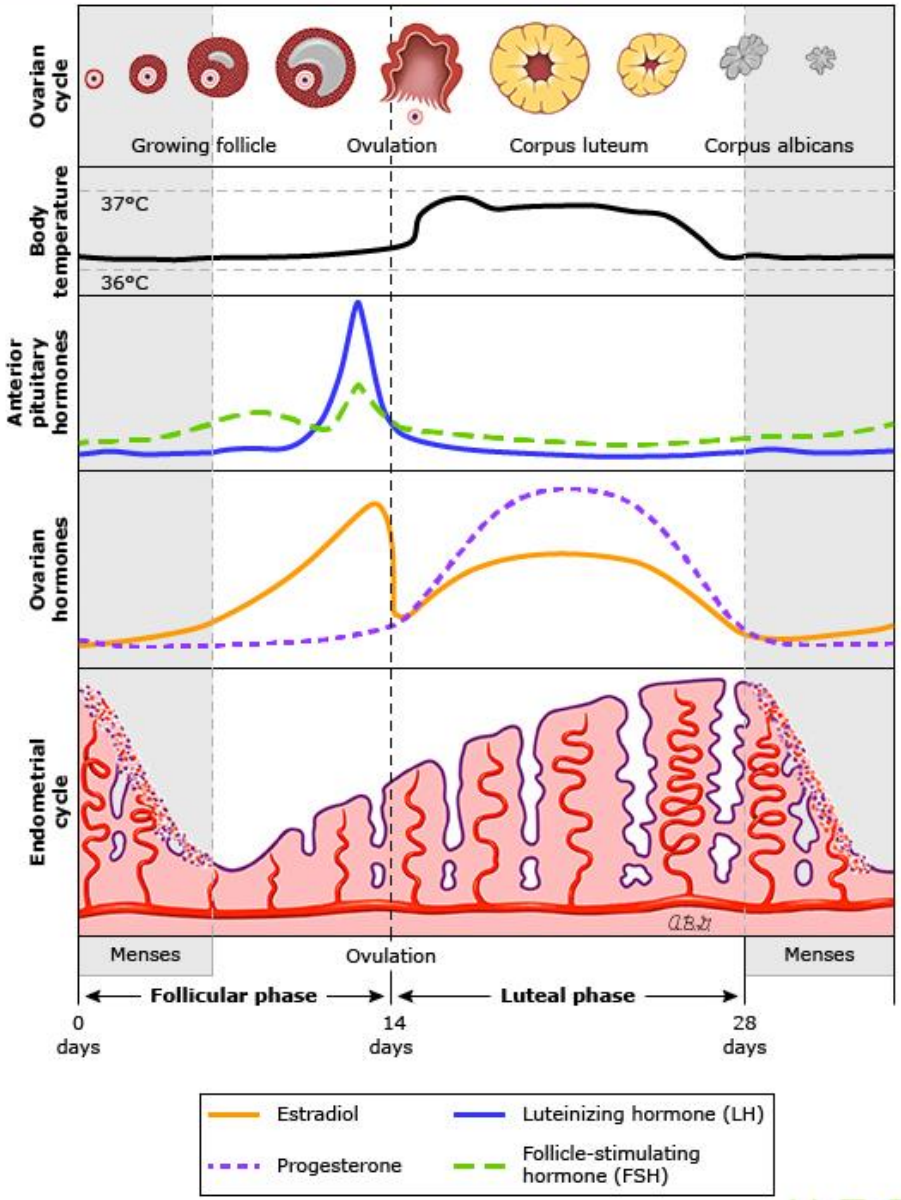
Objectives

1. Understand the classification of abnormal uterine bleeding
2. Be able to identify the most common etiologies based on age groups
3. Understand the components of evaluation and workup
4. Be familiar with medical management strategies in an outpatient setting

Background

- A common complaint affecting females of all ages
- Significantly impacts quality of life
- About 1/3 of all gynecologic visits
- 10 to 30% of reproductive-aged women
- Up to 50% of perimenopausal women

Menstrual cycle



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Normal Menstruation

- Interval: 28 days +/- 7 days (21-35 days)
- Duration of flow: 4-8 days
- Volume of blood loss: < 80 mL

- How to assess:
  - Menstrual calendar (or phone app)
  - Ask how frequently changing pads/tampons
    - More frequent than q3 hrs? How saturated?
  - Ask about clots
    - Larger than 1 inch diameter?

Definitions

- *Polymenorrhea*: more often than every 21 days
- *Oligomenorrhea*: less frequently than every 35 days
- *Menorrhagia*: > 80 mL in one period
  - In practice, based on patient's perception
- *Metrorrhagia*: bleeding between periods
- *Breakthrough bleeding*: associated with hormone use
- *Withdrawal bleeding:* predicted response to abrupt decline in progesterone levels

New classification

- No longer using "Dysfunctional uterine bleeding (DUB)"
- "Menorrhagia" → "Heavy menstrual bleeding (HMB)"
- "Metrorrhagia" →"Intermenstrual bleeding (IMB)"
- FIGO 2011: Nine categories of etiologies, arranged in acronym PALM-COEIN

"PALM- COEIN" Classification

Abnormal Uterine Bleeding (AUB)
- Heavy menstrual bleeding (AUB/HMB)
- Intermenstrual bleeding (AUB/IMB)

PALM: Structural Causes
Polyp (AUB-P)
Adenomyosis (AUB-A)
Leiomyoma (AUB-L)
Submucosal myoma (AUB-L_{SM})
Other myoma (AUB-L_{O})
Malignancy & hyperplasia (AUB-M)

COEIN: Nonstructural Causes
Coagulopathy (AUB-C)
Ovulatory dysfunction (AUB-O)
Endometrial (AUB-E)
Iatrogenic (AUB-I)
Not yet classified (AUB-N)

Etiology: PALM-COEIN

PALM: Structural Causes

- **P**olyp: Hyperplastic growth of endometrium that forms projection on endometrial surface.
- **A**denomyosis: Endometrial glands and stroma in uterine musculature
- **L**eiomyoma (fibroids): Benign tumors arising from smooth muscle cell of endometrium.
- **M**alignancy and Hyperplasia

Etiology: PALM-COEIN

COEIN: Nonstructural Causes

- **C**oagulopathy
- **O**vulatory Dysfunction: PCOS, abnormal hypothalamic-pituitary axis
- **E**ndometrial- infection, disrupted mediators of hemostasis
- **I**atrogenic
- **N**ot Yet Classified

History

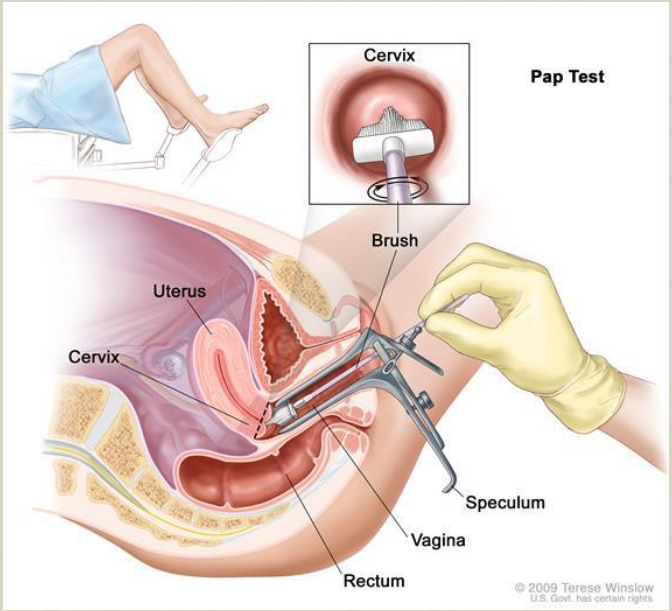
- Menstrual history
  - Age of menarche, LMP, bleeding pattern, timing, severity
- Pelvic pain?
- Sexual history, STI, postcoital bleeding?
- Pap history
- Family history
- Medications
  - warfarin, heparin, NSAIDs, contraceptives, supplements

Physical Exam

- Obesity
- Signs of PCOS (hirsuitism, acne)
- Signs of insulin resistance (acanthosis nigricans)
- Signs of thyroid disease (nodule, exopthalmos, weight gain/loss)
- Signs of hyperprolactinemia (galactorrhea, bilateral hemianopsia)
- Signs of blood disorder (petechiae, ecchymoses, gingival bleeding)

Pelvic Exam

- Speculum exam
  - Confirm source of bleeding
  - Vaginal lesion, cervical lesion/ mass, cervical polyp?
  - Current bleeding / clots in vaginal vault?
  - Foreign body?
  - Pap test
- Bimanual exam
  - Size, contour of uterus, fibroids?
  - Adnexal mass or tenderness



Laboratory Testing

- Pregnancy test! (urine or serum)
- CBC
- TSH
- Cervical cancer screening (Pap)
- Wet prep and STI screening (Trichomonas, GC/CT)

Box 1. Clinical Screening for an Underlying Disorder of Hemostasis in the Patient With Excessive Menstrual Bleeding ⇦

Initial screening for an underlying disorder of hemostasis in patients with excessive menstrual bleeding should be structured by medical history (positive screen comprises any of the following): *

Heavy menstrual bleeding since menarche

One of the following:

- Postpartum hemorrhage
- Surgery-related bleeding
- Bleeding associated with dental work

Two or more of the following symptoms:

- Bruising one to two times per month
- Epistaxis one to two times per month
- Frequent gum bleeding
- Family history of bleeding symptoms

*Patients with a positive screen should be considered for further evaluation, including consultation with a hematologist and testing of von Willebrand factor and ristocetin cofactor.

Reprinted from Kouides PA, Conard J, Peyvandi F, Lukes A, Kadir R. Hemostasis and menstruation: appropriate investigation for underlying disorders of hemostasis in women with excessive menstrual bleeding. Fertil Steril 2005;84(5):1345–51. [PubMed] [Full Text]

SCREENING FOR COAGULOPATHY

- CBC
- PT/ PTT

Up to 25% of women with chronic AUB have Von Willebrand Disease:

- vWF:RCo
- vWF:Ag
- FVIII

- Hematology referral

Age-Based Considerations

Adolescence

- Anovulation – immature hypothalamic-pituitary-ovarian axis
- Coagulation defects
- Pregnancy
- STI
- Sexual abuse

Age-Based Considerations

Reproductive age

- Pregnancy
- STI
- Structural causes (leiomyoma, polyps)
- Anovulatory cycles (PCOS)
- Hormonal contraception
- Endometrial hyperplasia

Perimenopause (40 to menopause)

- Anovulatory cycles (declining ovarian function)
- Structural causes (leiomyoma, polyps)
- Endometrial hyperplasia
- Endometrial cancer
- Endometrial atrophy

Age-Based Considerations

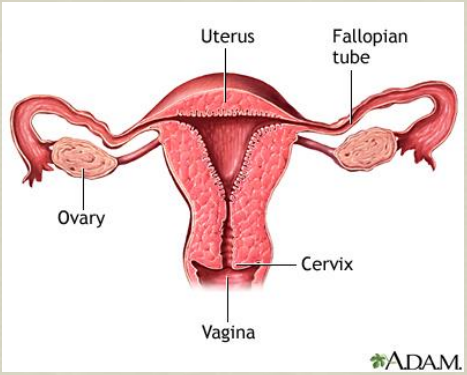
Post-menopause

- Most cases are benign:
  - Endometrial or vaginal atrophy
  - Benign endometrial polyps

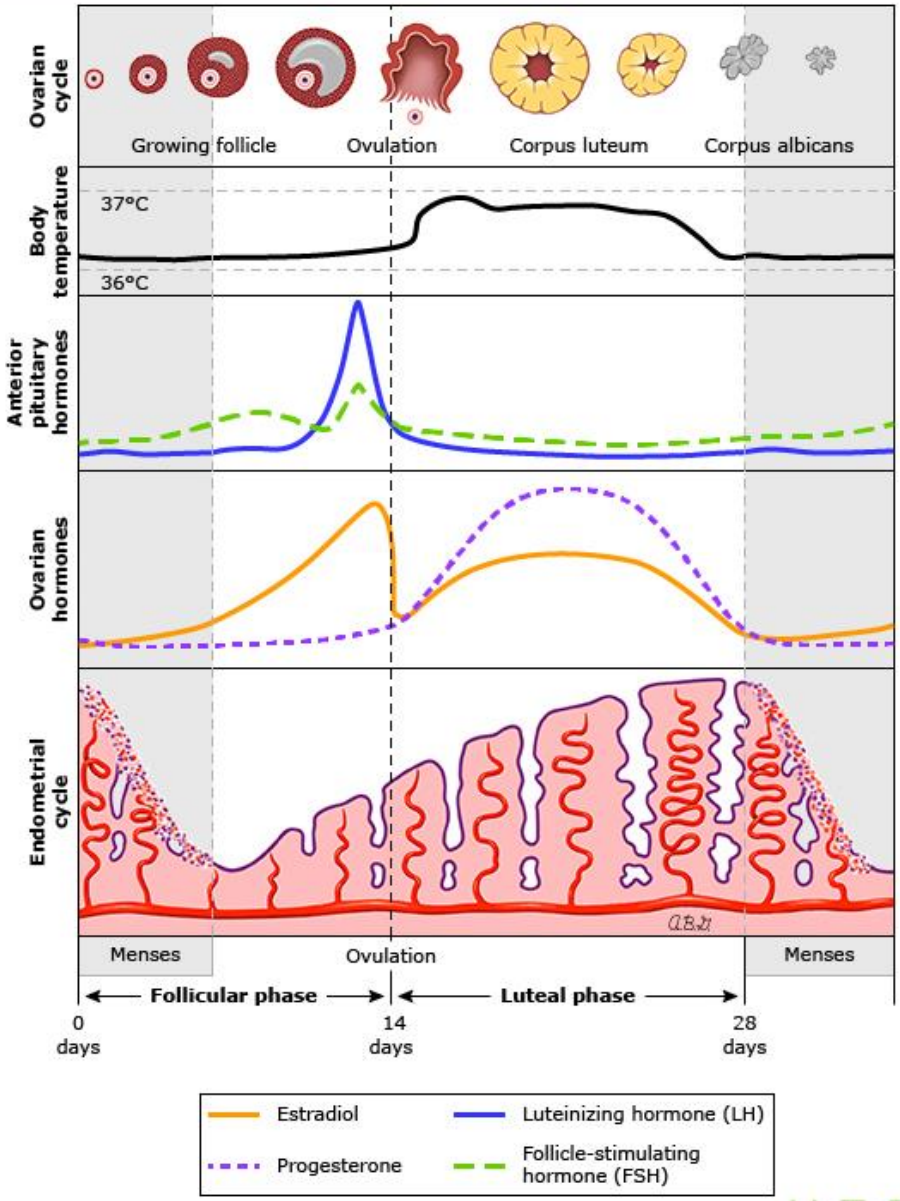
- Important to rule out malignancy
  - Endometrial carcinoma
  - Cervical, vulvar, vaginal neoplasms

Anovulatory Bleeding

- Ovulation is important for signaling the progesterone-induced effects at the endometrium
- Anovulation → chronic unopposed *estrogen* → *proliferative endometrium*
- Interruption in prostaglandin production, stromal breakdown, dilated and unstable endometrial blood vessels
- Bleeding can be severe and erratic
- Risk for endometrial hyperplasia / EIN and cancer
  - Treatment with progestins is protective



Menstrual cycle



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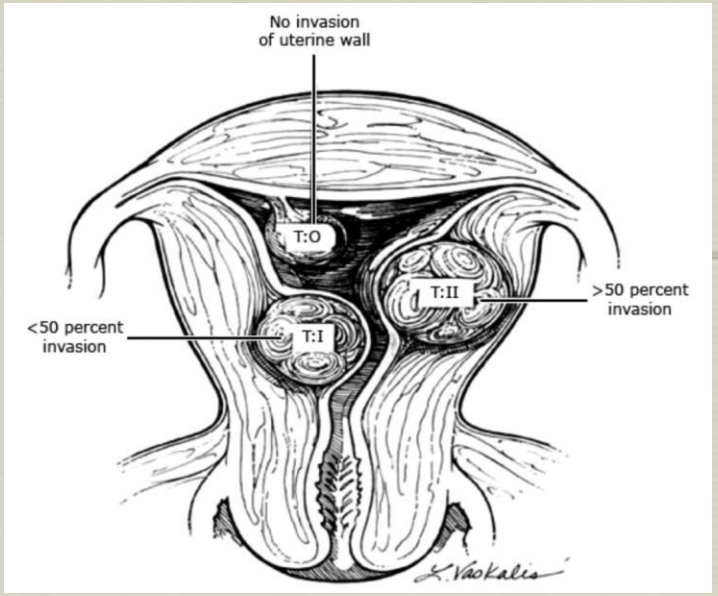
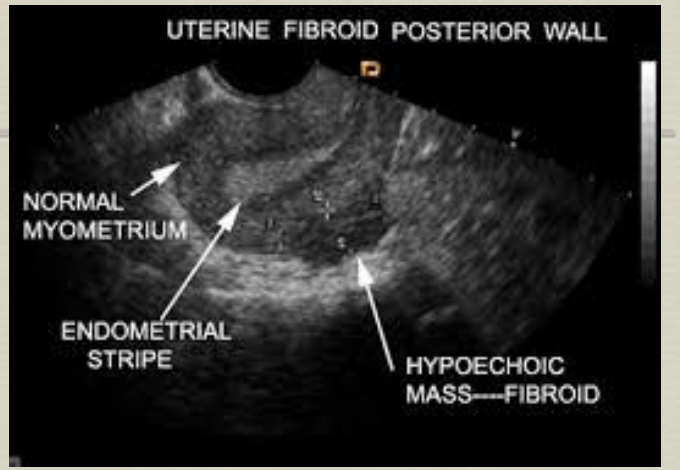
EVALUATION

Transvaginal ultrasound (TVUS)

- First-line evaluation tool to assess myometrium and endometrium
- Candidates for imaging:
  - Severe / acute bleeding
  - Abnormal physical exam
    - enlarged / globular uterus on bimanual (suspect leiomyoma or adenomyosis)
  - Persistent AUB / failed medical management

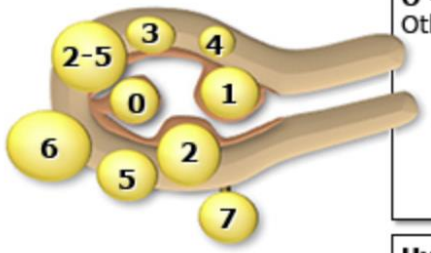
Evaluating Leiomyoma





http://www.meddean.luc.edu/

Leiomyoma subclassification system

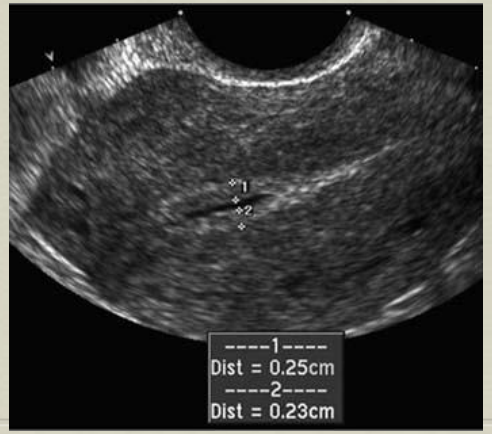


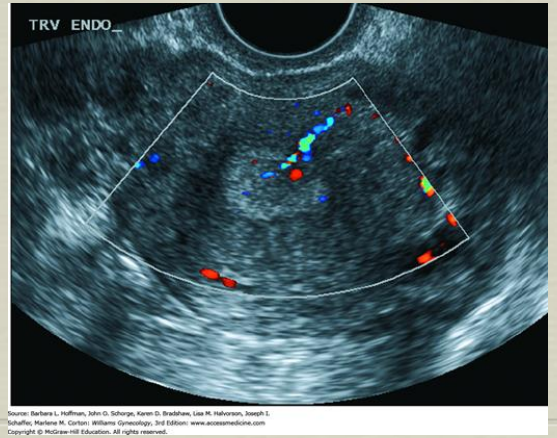
SM - Submucosal	0	Pedunculated intracavitary
	1	<50 percent intramural
	2	≥50 percent intramural
O - Other	3	Contacts endometrium; 100 percent intramural
	4	Intramural
	5	Subserosal ≥50 percent intramural
	6	Subserosal <50 percent intramural
	7	Subserosal pedunculated
	8	Other (specify, eg, cervical, parasitic)

Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below.	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

Endometrial thickness

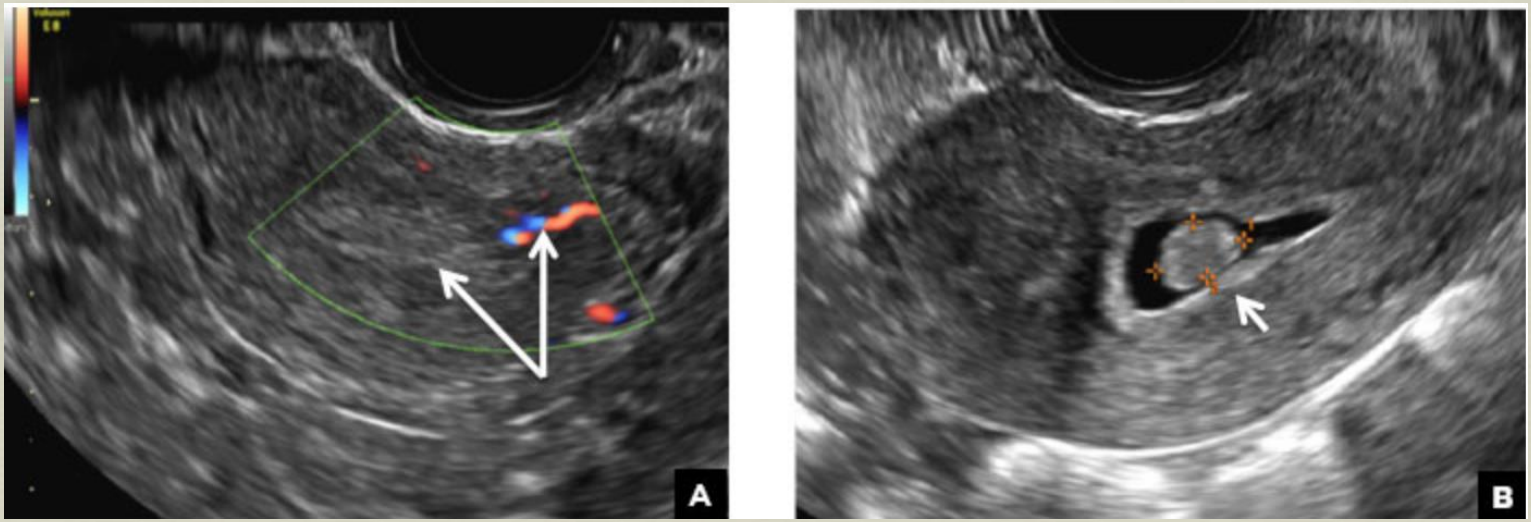
- Sagittal plane view of the uterus
- High negative predictive value for endometrial cancer in postmenopausal women
- > 4 mm is abnormal in postmenopausal. No standard threshold for premenopausal





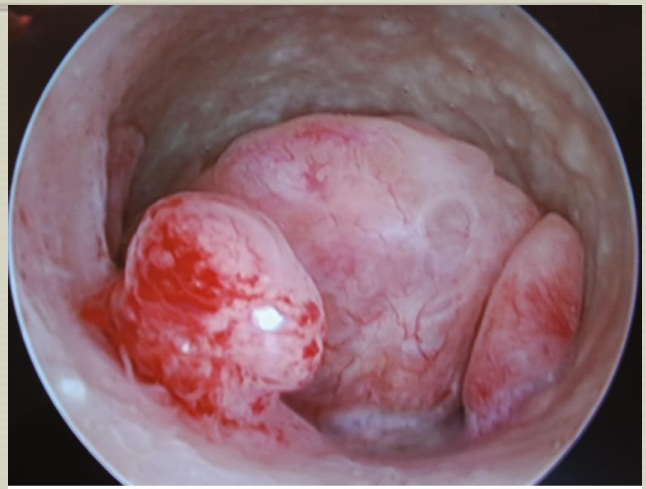
Saline-infusion Sonohysterography (SIS)

- When TVUS suggests polyp or submucosal leiomyoma, SIS may have better characterize
- Helpful for diagnosing intracavitary lesions



Hysteroscopy

- Gold standard for evaluation of uterine cavity
- Office or operating room
- Simultaneous sampling usually performed
- Advantage of treatment options at same time as diagnostic



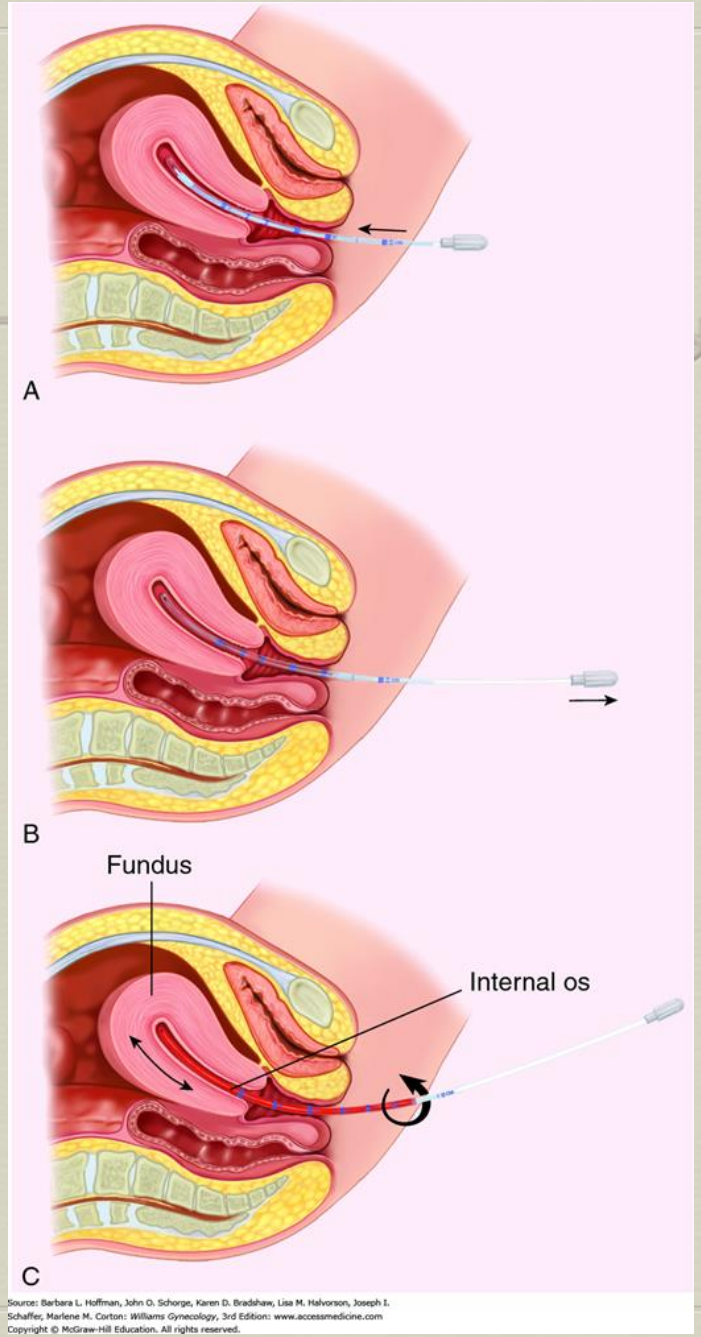
Source: Hoffman BL, Schorge JO, Schaffer JI, Halvorson LM, Bradshaw KD, Cunningham FG: *Williams Gynecology, 2nd Edition:* www.accessmedicine.com

Contemporaryobgyn.net

Endometrial sampling

- To rule out hyperplasia / malignancy
- Indications:
  - AUB and **> 45 years old**
  - Less than 45 years old if:
    - History of unopposed estrogen
    - Risk factors: PCOS, anovulatory, obesity, diabetes, hypertension, nulliparity, tamoxifen use
    - Persistent AUB / failed medical management

Endometrial biopsy (EMB)



- Usually performed in office with pipelle
- Sensitivity: better if global process
- Alternative: dilation and curettage (D&C) in operating room

TREATMENT

Medical Management

- NSAIDS
- Hormonal treatments:
  - High-dose estrogen
  - Combined hormonal contraceptives
  - Progestins
  - Intrauterine devices
- Tranexamic Acid (TXA)

TABLE 4

Treatment Options for Medical Management of Abnormal Uterine Bleeding

Drug	Suggested dosage	Notes
Acute bleeding		
Conjugated equine estrogen	Hemodynamically unstable: 25 mg intravenously every 4 to 6 hours for up to 24 hours Hemodynamically stable: 2.5 mg orally every 6 hours for 21 days	Follow treatment with a progestin to provoke withdrawal bleeding; do not use in patients at increased risk of thrombosis
Estrogen-progestin oral contraceptives	1 monophasic pill containing 35 mcg of ethinyl estradiol orally 3 times daily for 7 days	Other regimens also effective; do not use in patients at increased risk of thrombosis
Progestins	Norethindrone, 5 mg orally 3 times daily for 7 days	Other high-dose oral progestins are also effective
Tranexamic acid	10 mg per kg intravenously every 8 hours or 20 to 25 mg per kg orally every 8 hours	Faster onset if given intravenously; do not use in patients at increased risk of thrombosis
Chronic bleeding		
Depot medroxyprogesterone (Depo-Provera)	150 mg intramuscularly or 104 mg subcutaneously every 13 weeks	Unscheduled bleeding is a common initial adverse effect, but one-half of patients become amenorrheic after 12 months of use
Estrogen-progestin oral contraceptives	1 monophasic pill containing 35 mcg of ethinyl estradiol daily	Other routes (transdermal patch, intravaginal ring) are likely also effective; regimens with no or fewer hormone-free intervals may be more effective
Levonorgestrel	52-mg (20-mcg-per-day) intrauterine device (Mirena)	Effectiveness data are based primarily on trials involving the 20-mcg-per-day device; effect on bleeding suppression may wane before contraceptive effectiveness expires
Nonsteroidal anti-inflammatory drugs	Naproxen, 500 mg orally 2 times daily	Other oral nonsteroidal anti-inflammatory drugs are also effective; administer only while patient is bleeding; do not use in patients with coagulopathy
Progestins	Norethindrone, 2.5 to 5 mg orally once daily	Other oral progestins are also effective; administration during only the luteal phase is significantly less effective for treating heavy bleeding
Tranexamic acid (Lysteda)	1,000 to 1,500 mg orally 3 times daily	Faster onset if given intravenously; do not use in patients at increased risk of thrombosis

Note: The 2016 U.S. medical eligibility criteria for contraceptive use, published by the Centers for Disease Control and Prevention (https://www.cdc.gov/mmwr/volumes/65/rr/rr6503a1.htm), can be referenced to guide the use of the hormonal treatments listed in this table.

Information from references 37 through 42.

NSAIDS

- Ibuprofen, naproxen, mefanamic acid
- Scheduled dosing during menses
- Decreases prostaglandin synthesis in endometrium → vasoconstriction & reduced bleeding (by up to 33%)
- More effective than placebo but less effective than LNG-IUD and TXA

Estrogen

- Acute-onset, profuse heavy bleeding
- High-dose estrogen therapy
  - Premarin 2.5 mg PO every 6-12 hours
  - Premarin 25 mg IV every 4 hours up to 3 doses
  - Transition to oral taper with CHC once bleeding slows
- Antiemetic for associated nausea
- Contraindications: cardiovascular disease, HTN, hx VTE, thrombophilia, breast cancer, smoker over 35, migraines with aura

Combined hormonal contraception (CHC)

- Pills, patches, rings
- Estrogen and progesterone
- Thins the endometrium and protects from hyperplastic transition
- Reduces menstrual flow by 40-70%
- Low-dose, 20-35 micrograms of ethinyl estradiol

Scheduling CHCs

- Acute episode:
  - "OCP Taper" or Dose-diminishing regimens:
    - TID until bleeding stops, then BID x 3-7 days then once daily x 3 weeks then allow withdrawal bleed
    - TID for 7 days then daily x 3 weeks
    - 5-4-3-2-1
- Chronic bleeding:
  - Cyclic – monthly withdrawal bleed
  - Extended cycle – every 3-4 month withdrawal bleed
  - Continuous – hormone-pills only, skip placebo weeks altogether

Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion

Condition	Sub-Condition	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
		I	C	I	C	I	C	I	C	I	C	I	C
Age		Menarche to <20 yrs:**2**		Menarche to <20 yrs:**2**		Menarche to <18 yrs:**1**		Menarche to <18 yrs:**2**		Menarche to <18 yrs:**1**		Menarche to <40 yrs:**1**	
		≥20 yrs:**1**		≥20 yrs:**1**		18-45 yrs:**1**		18-45 yrs:**1**		18-45 yrs:**1**		≥40 yrs:**2**	
						>45 yrs:**1**		>45 yrs:**2**		>45 yrs:**1**			
Anatomical abnormalities	a) Distorted uterine cavity	**4**		**4**									
	b) Other abnormalities	**2**		**2**									
Anemias	a) Thalassemia	**2**		**1**		**1**		**1**		**1**		**1**	
	b) Sickle cell disease‡	**2**		**1**		**1**		**1**		**1**		**2**	
	c) Iron-deficiency anemia	**2**		**1**		**1**		**1**		**1**		**1**	
Benign ovarian tumors	(*including cysts*)	**1**		**1**		**1**		**1**		**1**		**1**	
Breast disease	a) Undiagnosed mass	**1**		**2**		**2***		**2***		**2***		**2***	
	b) Benign breast disease	**1**		**1**		**1**		**1**		**1**		**1**	
	c) Family history of cancer	**1**		**1**		**1**		**1**		**1**		**1**	
	d) Breast cancer‡												
	i) Current	**1**		**4**		**4**		**4**		**4**		**4**	
	ii) Past and no evidence of current disease for 5 years	**1**		**3**		**3**		**3**		**3**		**3**	
Breastfeeding	a) <21 days postpartum					**2***		**2***		**2***		**4***	
	b) 21 to <30 days postpartum												
	i) With other risk factors for VTE					**2***		**2***		**2***		**3***	
	ii) Without other risk factors for VTE					**2***		**2***		**2***		**3***	
	c) 30-42 days postpartum												
	i) With other risk factors for VTE					**1***		**1***		**1***		**3***	
	ii) Without other risk factors for VTE					**1***		**1***		**1***		**2***	
	d) >42 days postpartum					**1***		**1***		**1***		**2***	
Cervical cancer	Awaiting treatment	**4**	**2**	**4**	**2**	**2**		**2**		**1**		**2**	
Cervical ectropion		**1**		**1**		**1**		**1**		**1**		**1**	
Cervical intraepithelial neoplasia		**1**		**2**		**2**		**2**		**1**		**2**	
Cirrhosis	a) Mild (*compensated*)	**1**		**1**		**1**		**1**		**1**		**1**	
	b) Severe‡ (*decompensated*)	**1**		**3**		**3**		**3**		**3**		**4**	
Cystic fibrosis‡		**1***		**1***		**1***		**2***		**1***		**1***	
Deep venous thrombosis (DVT)/Pulmonary embolism (PE)	a) History of DVT/PE, not receiving anticoagulant therapy												
	i) Higher risk for recurrent DVT/PE	**1**		**2**		**2**		**2**		**2**		**4**	
	ii) Lower risk for recurrent DVT/PE	**1**		**2**		**2**		**2**		**2**		**3**	
	b) Acute DVT/PE	**2**		**2**		**2**		**2**		**2**		**4**	
	c) DVT/PE and established anticoagulant therapy for at least 3 months												
	i) Higher risk for recurrent DVT/PE	**2**		**2**		**2**		**2**		**2**		**4***	
	ii) Lower risk for recurrent DVT/PE	**2**		**2**		**2**		**2**		**2**		**3***	
	d) Family history (*first-degree relatives*)	**1**		**1**		**1**		**1**		**1**		**2**	
	e) Major surgery												
	i) With prolonged immobilization	**1**		**2**		**2**		**2**		**2**		**4**	
	ii) Without prolonged immobilization	**1**		**1**		**1**		**1**		**1**		**2**	
	f) Minor surgery without immobilization	**1**		**1**		**1**		**1**		**1**		**1**	
Depressive disorders		**1***		**1***		**1***		**1***		**1***		**1***	

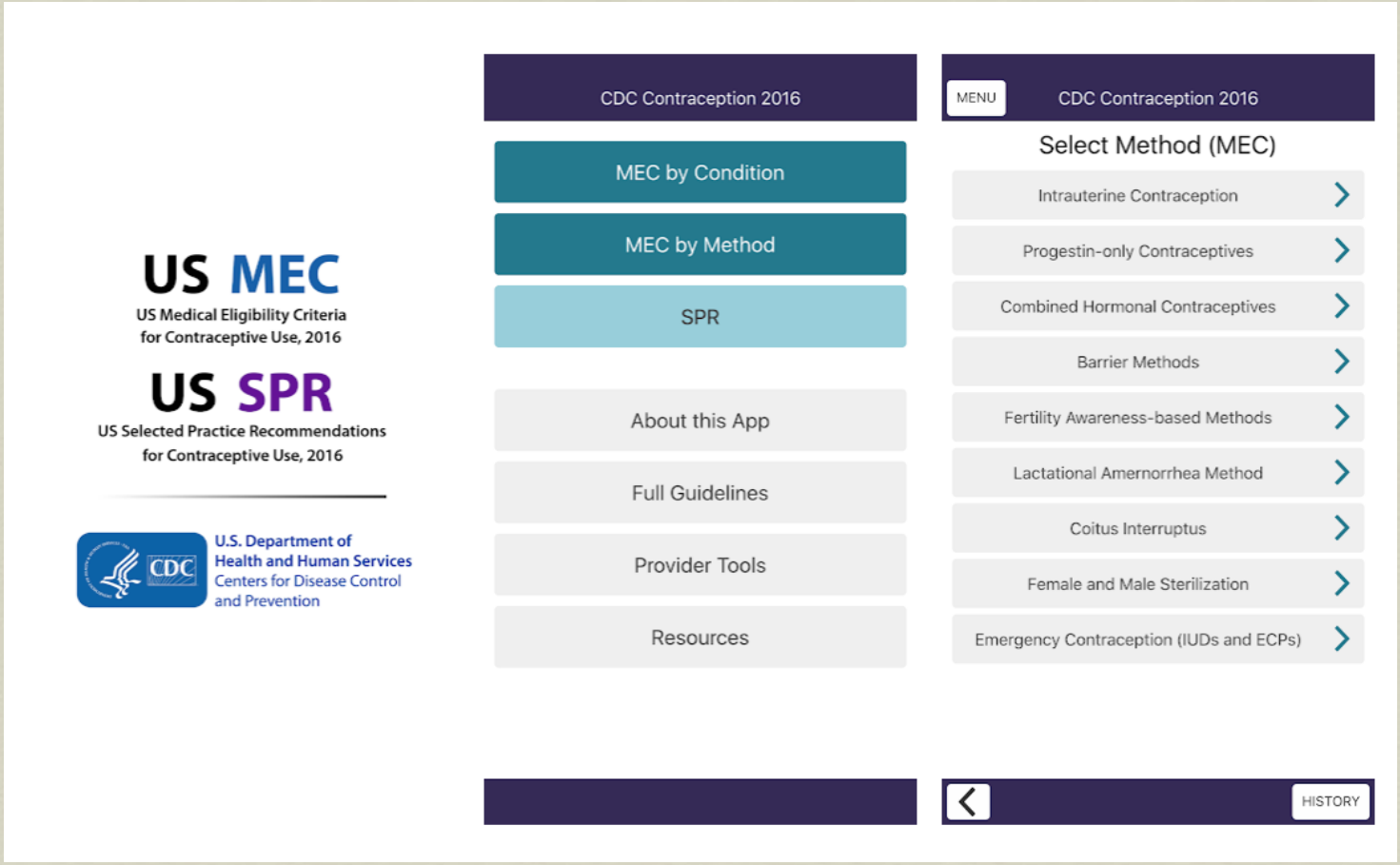
Condition	Sub-Condition	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
		I	C	I	C	I	C	I	C	I	C	I	C
Diabetes	a) History of gestational disease	**1**		**1**		**1**		**1**		**1**		**1**	
	b) Nonvascular disease												
	i) Non-insulin dependent	**1**		**2**		**2**		**2**		**2**		**2**	
	ii) Insulin dependent	**1**		**2**		**2**		**2**		**2**		**2**	
	c) Nephropathy/retinopathy/neuropathy‡	**1**		**2**		**2**		**3**		**2**		**3/4***	
	d) Other vascular disease or diabetes of >20 years' duration‡	**1**		**2**		**2**		**3**		**2**		**3/4***	
Dysmenorrhea	Severe	**2**		**1**		**1**		**1**		**1**		**1**	
Endometrial cancer‡		**4**	**2**	**4**	**2**	**1**		**1**		**1**		**1**	
Endometrial hyperplasia		**1**		**1**		**1**		**1**		**1**		**1**	
Endometriosis		**2**		**1**		**1**		**1**		**1**		**1**	
Epilepsy‡	(*see also Drug Interactions*)	**1**		**1**		**1***		**1***		**1***		**1***	
Gallbladder disease	a) Symptomatic												
	i) Treated by cholecystectomy	**1**		**2**		**2**		**2**		**2**		**2**	
	ii) Medically treated	**1**		**2**		**2**		**2**		**2**		**3**	
	iii) Current	**1**		**2**		**2**		**2**		**2**		**3**	
	b) Asymptomatic	**1**		**2**		**2**		**2**		**2**		**2**	
Gestational trophoblastic disease‡	a) Suspected GTD (immediate postevacuation)												
	i) Uterine size first trimester	**1***		**1***		**1***		**1***		**1***		**1***	
	ii) Uterine size second trimester	**2***		**2***		**1***		**1***		**1***		**1***	
	b) Confirmed GTD												
	i) Undetectable/non-pregnant ß-hCG levels	**1***	**1***	**1***	**1***	**1***		**1***		**1***		**1***	
	ii) Decreasing ß-hCG levels	**2***	**1***	**2***	**1***	**1***		**1***		**1***		**1***	
	iii) Persistently elevated ß-hCG levels or malignant disease, with no evidence or suspicion of intrauterine disease	**2***	**1***	**2***	**1***	**1***		**1***		**1***		**1***	
	iv) Persistently elevated ß-hCG levels or malignant disease, with evidence or suspicion of intrauterine disease	**4***	**2***	**4***	**2***	**1***		**1***		**1***		**1***	
Headaches	a) Nonmigraine (mild or severe)	**1**		**1**		**1**		**1**		**1**		**1***	
	b) Migraine												
	i) Without aura (includes menstrual migraine)	**1**		**1**		**1**		**1**		**1**		**2***	
	ii) With aura	**1**		**1**		**1**		**1**		**1**		**4***	
History of bariatric surgery‡	a) Restrictive procedures	**1**		**1**		**1**		**1**		**1**		**1**	
	b) Malabsorptive procedures	**1**		**1**		**1**		**1**		**3**		COCs: **3** P/R: **1**	
History of cholestasis	a) Pregnancy related	**1**		**1**		**1**		**1**		**1**		**2**	
	b) Past COC related	**1**		**2**		**2**		**2**		**2**		**3**	
History of high blood pressure during pregnancy		**1**		**1**		**1**		**1**		**1**		**2**	
History of Pelvic surgery		**1**		**1**		**1**		**1**		**1**		**1**	
HIV	a) High risk for HIV	**2**	**2**	**2**	**2**	**1**		**2***		**1**		**1**	
	b) HIV infection					**1***		**1***		**1***		**1***	
	i) Clinically well receiving ARV therapy	**1**	**1**	**1**	**1**	If on treatment, see Drug Interactions							
	ii) Not clinically well or not receiving ARV therapy‡	**2**	**1**	**2**	**1**	If on treatment, see Drug Interactions							

Key:

1 No restriction (method can be used)	**3** Theoretical or proven risks usually outweigh the advantages
2 Advantages generally outweigh theoretical or proven risks	**4** Unacceptable health risk (method not to be used)

Abbreviations: C=continuation of contraceptive method; CHC=combined hormonal contraception (pill, patch, and, ring); COC=combined oral contraceptive; Cu-IUD=copper-containing intrauterine device; DMPA = depot medroxyprogesterone acetate; I=initiation of contraceptive method; LNG-IUD=levonorgestrel-releasing intrauterine device; NA=not applicable; POP=progestin-only pill; P/R=patch/ring ‡ Condition that exposes a woman to increased risk as a result of pregnancy. *Please see the complete guidance for a clarification to this classification: www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm.

CDC U.S. Medical Eligibility Criteria for Contraceptive Use (U.S. MEC)



Progestin Therapy

- **Medroxyprogesterone acetate (Provera)**
  - Acute episode taper: 20 mg TID x 7 days then daily x 3 weeks
  - 5 to 30mg daily
- **Norethindrone acetate (Aygestin)**
  - More potent
  - 5 mg daily, up to TID
- **Megestrol acetate (Megace)**
- Continuous dosing may be more effective than cyclic
- Side effects: mood changes, bloating, weight gain, headaches

Depo Injection

- Depot medroxyprogesterone acetate
- Intramuscular or subcutaneous injection
- Patient selection:
  - Contraindication to estrogen
  - Prefer this method of contraception
- About 50% reduction in bleeding within 2 months
- Side effects: weight gain, delayed return of fertility

Intrauterine Devices (IUD)

- Levonorgestrel (LNg52/5) is FDA-approved for heavy menstrual bleeding
  - High local progestin effect → thinned endometrium
  - Reduces menstrual blood loss by 71-95%
  - Majority have infrequent light bleeding/spotting or amenorrhea (after 3-6 months)

- Protection against endometrial hyperplasia and cancer
- Increasingly being used before moving to surgical options

Subdermal Implant

- Etonorgestrel contraceptive
- Unpredictable light bleeding/spotting first 3-6 months
- Treatment of breakthrough bleeding:
  - Oral estradiol 1 mg daily x 10 days
  - Short-course NSAIDs
  - Doxycycline 100mg BID x 10 days

Tranexamic Acid (TXA)

- For patients who do not desire or cannot take hormonal options
- Antifibrinolytic agent
- Approved by FDA for HMB in 2009
  - 1300mg TID x 5 days (during menses)
- Possible thrombosis risk with long-term use
- More effective than NSAIDs but less effective than LNG-IUD

Failed Medical Management

- Surgical treatment options:
  - Endometrial ablation
  - Uterine artery embolization
  - Myomectomy
  - Hysterectomy

Referral to OB/GYN

- Surveillance of medical management
- Failed medical management
- Difficult IUD insertion or endometrial sampling
- Structural cause possibly needing surgery (polyps, large leiomyoma)
- Postmenopausal bleeding

Thank you!

- Questions?
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