

## ***Abnormal Uterine Bleeding (AUB)***

***FMF 2019***

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### ***Disclosure:***

- ***This program has received no financial or in-kind support through any commercial organization.***
- ***Potential for conflict(s) of interest:***
  - ***Bayer/Berlex (makers of Mirena) which will be discussed in this session; the company has provided unrestricted educational grants to fund the Benign Uterine Conditions project sponsored by OCFP from 2005-2014***

### ***Objectives***

- Define AUB pre-, peri- and postmenopausal
- Explore etiology/pathophysiology of AUB
- Review assessment tools
- Discuss treatment options
- Apply learning pearls through clinical cases

### ***Normal Menstrual Physiology***

- average cycle 28-35 d, 14-21 d in follicular phase and 14 d in luteal phase (rel. constant)
- relatively little cycle variability ages 20-40
- cycle varies 5-7 y after menarche and for up to 10 y before menopause
- cycle often shortens as women approach menopause

### ***AUB Premenopausal Women - Definition***

Any variation from the normal menstrual cycle, including changes in regularity and frequency of menses, in duration of flow, or in amount of blood loss

### ***AUB Premenopausal Women – Categories***

- Ovulatory AUB*** usually regular and often associated with premenstrual symptoms and dysmenorrhea
- Anovulatory AUB*** more common near menarche and the perimenopause; often irregular, heavy, and prolonged flow; more likely to be associated with endometrial hyperplasia and cancer

### ***AUB Classification System – FIGO 2011 (non-pregnant premenopausal women)***

#### ***Structural***

- P – polyp***
- A – adenomyosis***
- L – leiomyoma***
- M - malignancy***

#### ***Non-Structural***

- C – coagulopathy***
- O – ovulatory dysf.***
- E – endometrium***
- I – iatrogenic***
- N – not yet classified***

### ***Abnormal Genital Bleeding/AUB Premenopausal Women - Differential***

- Anatomic categorisation:*
- Uterus* – pregnancy, menorrhagia, anovulatory – periods of transition in reproductive life including adolescence and perimenopause; PCO, endocrine, other; fibroid, polyp, adenomyosis, structural abnormalities; Ca; FB; infections like endometritis/PID; bleeding disorders; meds; ruptured ovarian cyst
- Cervix* – polyps, cervicitis, ectropian, Ca, prolapse
- Vagina* – vaginitis, trauma, Ca, fistulas, FB benign neoplasms, cysts, radiation, atrophy
- Vulva* – infection, benign growths, Ca, trauma
- \*\*\*Neighbouring structures* – bowel, urethra, bladder, skin eg. Crohn's, lichen sclerosis
- Endocrine Causes* - In adolescent within the first 1.5-2 years following menarche, the AUB may be caused by an immature HPO axis\*\*\*
- Other Endocrine Causes* - PCOS, CAH, hyperprolactinemia, Cushings, thyroid dysfunction, pituitary tumors
- Meds:* see list
- Anticoagulants
- Antidepressants (SSRIs, TCAs)
- Hormonal contraceptives
- Tamoxifen
- Antipsychotics (first generation, risperidone)
- Corticosteroids
- Herbs: ginseng, chasteberry, danshen
- Infections:* vulva, vagina, cervix etc.
- Bleeding disorders*
- Systemic disorders* eg. DM, renal disease, SLE, Ca
- Structural lesions* eg. fibroids, polyps
- Other Causes:* FB, trauma

### ***Abnormal Genital Bleeding/AUB - Premenopausal Women - History***

- ***Systemic:*** SOB, dizziness – consider anemia; Sx of hypothyroidism, hyperprolactinemia, coagulopathy, PCOS, adrenal or hypothalamic disorders
- ***GU Sx:*** discharge, change in odor, pelvic pain/pressure
- ***Sexual Hx:*** contraception, pregnancy risk, STIs, cervical screening
- ***Reproductive Hx:*** family planning, infertility
- ***Social Hx:*** impact on QOL including sexual function
- ***PMH:*** hormonally dependent tumours, thromboembolic disease, or cardiovascular problems – affects Rx choices
- ***FH:*** inherited coagulation disorders, PCOS, endometrial or colon cancer

### ***AUB Premenopausal Women - Exam***

- Vital signs
- Weight/BMI
- Thyroid

- Skin (pallor, bruising, striae, hirsutism, petechiae)
- Breast (galactorrhea, masses)
- Abdomen (mass, hepatosplenomegaly)
- GU: inspection: vulva, vagina, cervix, anus, and urethra; Bimanual examination of uterus and adnexal structures; Pap smear, cervical cultures if STI risk

***AUB Management Premenopausal Women - SOGC Guidelines May 2013***

- Investigations:*
- CBC
- Pregnancy test (urine or serum) if needed
- TSH if there is other evidence of thyroid disease
- Coagulation tests if FH of coagulopathy or if woman has had AUB since menarche – ie. VWD
- FSH – measure twice 1 month apart; irregular bleeding could herald premature ovarian insufficiency (my suggestion)
- Imaging:*
- Transvaginal US (TVUS) is first line
- Saline infusion sonogram (SIS) and diagnostic hysteroscopy to be used for Dx of intrauterine abnormalities such as submucosal fibroids or polyps or abnormally structured uterus
- TVUS endometrial thickness in pre-menopausal woman:** follicular phase: as thin as 4 mm; luteal phase: up to 16 mm
- MRI rarely used to assess the endometrium in AUB but helpful pre-op to map exact location of fibroids and may also be useful in assessing the endometrium when TVUS or instrumentation of the uterus (i.e. congenital anomalies) cannot be performed
- Fibroids*** –
- Benign smooth muscle tumors of uterus
- If asymptomatic do not require treatment
- Symptoms: pain/pressure, bowel and bladder dysfunction, AUB/anemia & infertility
- Physical exam and US
- Must **SAMPLE ENDOMETRIUM** if AUB and risk factors for cancer present
- Tissue sampling:
- Endometrial biopsy (Bx) 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 for endometrial cancer

***Risk Factors Endometrial Ca***

- Fam. Hx endometrial or colon Ca (HNPCC)***
- Age > 40***
- Diabetes type II***
- PCOS/Anovulatory cycles***
- Obesity (BMI > 30 kg/m<sup>2</sup>)***
- Nulliparity***
- Tamoxifen***

- Indications for tissue sampling:**
- Any persistent change in menstrual cycle, frequency, duration, flow**
- \*\*\*The average age for women with endometrial cancer is 61 years, but 5% to 30% of cases occur in premenopausal women

### **Endometrial Biopsy (Bx)**

- Purpose is to evaluate the endometrial lining for Ca, hyperplasia and normal endometrial growth when assessing for infertility and luteal phase defect
- Sensitivity to detect abnormalities 81-96 %
  - Comparable to D&C; may be better
  - Less reliable than hysteroscopy
- Adequate sample obtained > 85%
- Office endometrial Bx should replace D&C as initial assessment of endometrium
- Focal lesions of endometrium requiring Bx should be managed through hysteroscopy-guided evaluation

### **Interpreting Endometrial Biopsy**

- Normal
  - Symptoms resolve→follow
  - Symptoms persist→TVUS
- Unable to perform/inadequate sample
  - Repeat
  - TVUS
- Hyperplasia without atypia
  - Medroxyprogesterone (Provera) 10mg od or micronised progesterone (Prometrium) 200 mg po/pv for 30 d or cyclic 12-14 d x 3- 6 months
  - Repeat biopsy 3- 6 months later
- Hyperplasia with atypia, cancer→refer

### **Medications for AUB**

- NSAIDS**
- Tranexamic acid (Cyklokapron)**
- OCP (combined)**
- Progestins (oral, IM)**
- GnRH agonist**
- Danazol**
- Progestin intrauterine system (IUS Mirena)**
- Ulipristal**

Non-hormonal options such as **NSAIDs** (reduce bleeding by 25-35%) and antifibrinolytics (tranexamic acid or Cyklokapron) can be used effectively to treat heavy menstrual bleeding that is mainly cyclic or predictable in timing

- Tranexamic acid (Cyklokapron):**
- Synthetic derivative of lysine (amino acid)
- Antifibrinolytic effect through reversible blockade on production of plasminogen
- No increase in TE; dysmenorrhea not affected
- s/e: nausea, leg cramps in 30%
- Dose: 2-3 tabs (500 mg) tid prn - start Rx at onset of bleeding for heaviest days
- Cost: \$1/tab generic; \$1.50 trade name
- \*\*Calendar BMJ 1970;24:214-6

- Combined OCPs** (reduce bleeding by 40-50%), 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
- \*\*\*\*In premenopausal women who have regular periods, cyclic luteal-phase **progestins** do not effectively reduce blood loss and therefore should not be used as a specific treatment for heavy menstrual bleeding
- GnRH agonists:**
  - induce reversible hypoestrogenic state – like “temporary menopause”
  - Decrease fibroids and uterine volume by 40-60% (reverses within months of stopping Rx) which decreases blood flow
  - s/e: hot flashes; decreased bone density
  - \*\*Friedman Obs Gyne 1991;77:720-5.
  - Leuprolide (Lupron) depot given IM 3.75 mg q monthly or 11.25 mg q 3 months for 6-12 months – duration of Rx based on individual woman
  - Add back therapy – progestin +/- estradiol transdermal preferred – patch/gel
- Danazol:**
  - Synthetic steroid with mild androgenic properties
  - Inhibits steroid production in the ovary
  - 80% reduction in menstrual blood loss
  - 20% of patients develop amenorrhea; 70 % of women develop oligomenorrhea
  - s/e – none in 50%; 20% report minor concerns like weight gain 2-6 lbs.
  - Dose: 100-400 mg od for three months

**Progestin intrauterine system** (ie. Mirena) has outcomes similar to endometrial ablation for women with heavy menstrual bleeding and thus may be considered prior to surgical intervention (also gives 40% decrease in dysmenorrhea)

- Danazol and gonadotropin-releasing hormone (GnRH) agonists to be used when other medical or surgical treatments have failed or are contraindicated
- women receiving GnRH agonist for longer than 6 months should be prescribed add-back hormone therapy if not already initiated with GnRH agonist commencement

#### **Progestin Intrauterine System (Mirena)**

- Breakthrough bleeding up to 6 months
  - followed by amenorrhea in 70 % by one year
- Mild cramps upon insertion
- Possible progesterone side effects from systemic absorption in first few weeks
- Expulsion, perforation rate (1/1000)
- T-shaped device which releases 20 ug/day of levonorgestrel locally in the uterine cavity
- Inserted in the office, similar to regular IUD
- Lasts 5 years; total of 52 mg levonorgestrel in device
- \$420 Can. (2019)
- Device covered on ODB
- OHIP billing: G378 & E430
- Insert early in cycle (days 4-8) to reduce spotting/bleeding
- Consider priming with OCP x 1-2 months if severe menorrhagia

- Warn patient about potential side-effects
- Ovulation will continue normally in most ♀ (75%)
- Immediately effective as contraceptive, and immediately reversible
- May get free replacement if dropped, expelled, or causing pain
- If endometritis; treat with Mirena in-situ
- May do PAP, SIS, and endometrial biopsy with Mirena in-situ
- Ulipristal**
- Selective progesterone receptor modulator (think SPRM)
- Side effects – abdominal pain, irregular bleeding/amenorrhea, headaches, nausea
- metabolized CYP3A4; avoid in women with severe liver disease, lactation, < 18
- could interact with substrates of CYP3A4, like [rifampicin](#), [phenytoin](#), [St John's wort](#), [carbamazepine](#), [ritonavir](#), hormonal contraceptives and [progestogens](#) such as [levonorgestrel](#), [glucocorticoids](#)
- As a SPRM, ulipristal acetate has [partial agonistic](#) as well as [antagonistic](#) effects on the [progesterone receptor](#)
- binds to the [glucocorticoid receptor](#)
- has no relevant affinity to the [estrogen](#), [androgen](#) and [mineralocorticoid receptors](#)
- mechanism might consist of blocking or delaying [ovulation](#) and of delaying the maturation of the [endometrium](#)
- Used for emergency contraception in over 50 countries at a dose of 30 mg tablet within 120 hours (5 days) after unprotected sex or contraceptive failure
- has been shown to prevent about 60% of expected pregnancies (more pregnancies than emergency contraception with levonorgestrel)
- pre-operative treatment of uterine fibroids in reproductive age women 5 mg/day for 3 months effectively controlled excessive bleeding due to uterine fibroids and reduced the size of the fibroids
- 2 interrupted 3-month Rx courses of ulipristal acetate 10 mg resulted in amenorrhea at the end of the first Rx course in 79.5%, at the end of the second course in 88.5% of subjects; fibroid volume reduction observed during the first treatment course (-41.9%) was maintained during the second one (-43.7%)

***With the exception of NSAIDs, same medical agents used to treat heavy menstrual bleeding among women with normal coagulation can effectively be used in the setting of inherited bleeding disorders***

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- Acute heavy AUB**
- Acute heavy menstrual bleeding should be managed promptly and systematically to minimize patient morbidity and the need for blood transfusion using high-dose estrogen and tranexamic acid
- Consider possible bleeding disorder in recently menarchal adolescents
- Medical management of acute severe AUB can involve the use of CES 25 mg iv q6h or 2.5 mg po qid; increase to 5 mg po qid in 24 hrs. if needed
- Oral Rx with OCP 100 ug ethinyl estradiol
- Can use 2 tabs of 35 ug ethinyl estradiol OCP daily for 5d; go to 1 tab od (start with iv Rx)
- \*Nausea common S/E high-dose estrogen

- Contraindications for high dose E Rx: VTE, inherited thrombophilias, MI, CVA, Ca (women at high risk for thrombosis)
- Tranexamic acid may also be started at a dose of 1000 mg q6h iv/po
- high-dose progestins such as MPA (10 to 20 mg twice daily) or megestrol acetate (20 to 60 mg twice daily)

### ***Surgery***

- D&C:*** out of favor; bleeding decreased for a couple of months after procedure and then returns to pre-treatment levels
- Endometrial ablation:*** usual outcome markedly decreased menstrual flow rather than amenorrhea; ie. balloon, microwave, and radiofrequency ablation
- Hysterectomy***
- Endometrial Ablation:***
  - surgical destruction of the endometrium
  - Resectoscopic* ablation performed under hysteroscopic guidance, using resectoscopic instruments to ablate or resect the endometrium
  - Non-resectoscopic* ablation performed with a disposable device which is inserted into the uterine cavity and delivers energy to uniformly destroy the uterine lining
  - Designed for women who have completed their families
  - Contraception still required for those who are sexually active
  - Pre-op: biopsy needed to rule out Ca and hyperplasia
  - Post-op: cramping and vaginal discharge
  - Presence of submucosal fibroids make procedure less effective; may need to be removed prior to ablation
  - Endometrial preparation using GnRH agonists recommended prior to ablation (using either resectoscope or non-resectoscope procedure)
- Hysterectomy (minimally invasive):***
  - option in women who desire definitive therapy and who are willing to accept the risk of perioperative complications
- Endometrial ablation vs. hysterectomy:***
  - ablation less costly, lower complication rates of bleeding and infection (sexual effects?), less recovery time post-op
  - At 2 yrs. post-op patient satisfaction favored hysterectomy (79 vs. 71%) but at 4 yrs. basically the same

### ***AUB in the Postmenopausal Women (PMW)***

- Postmenopausal bleeding (PMB) refers to any uterine bleeding in a menopausal woman (other than that expected with progestin withdrawal in cyclic combined postmenopausal hormone therapy)
- Unexpected vaginal bleeding in PMW must be investigated
- Vaginal bleeding occurs in 4-11% of PMW
- In PMW with vaginal bleeding, the risk of uterine Ca is 7.3% if the endometrial thickness or echo (EE) is >5 mm and <0.07% if EE is thin < or = 5 mm\*\*
- As age increases the risk for endometrial Ca for each EE measurement increases
- \*\*Smith-Bridman Ultrasound Obstet Gynecol 2004;24(5):558

*Causes of AUB in PMW*

- |  |     |
|--|-----|
| <input type="checkbox"/> Atrophy**               | 59% |
| <input type="checkbox"/> Endometrial Polyp       | 12% |
| <input type="checkbox"/> Endometrial Hyperplasia | 10% |
| <input type="checkbox"/> Endometrial Cancer      | 10% |
| <input type="checkbox"/> Hormonal effect         | 7%  |
| <input type="checkbox"/> Cervical Cancer         | <1% |
| <input type="checkbox"/> Other                   | 2%  |

*Source: Karlsson et al 1995*

*Endometrial Biopsy Indications in PMW*

- Vaginal bleeding >12 months after LMP
- Vaginal bleeding >6-12 months after initiating PM-HT
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- If AUB occurs, evaluate endometrium and uterine cavity as well as the genital tract and external genitalia
- Either endometrial Bx, TVUS or both can be done to initially assess the endometrium
- Can base choice of first investigation upon patient preference, physician comfort with procedure, TVUS availability

*\*\*\*If TVUS done as initial investigation, endometrial cancer can reasonably be excluded in postmenopausal women with a thin (<5 mm), homogeneous endometrium*

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- Endometrial tissue sampling required if:
- Endometrial thickness > 4 mm
- Endometrium heterogeneous or irregular in thickness within various areas of the cavity
- Endometrium not adequately examined
- PMW bleeds persistently
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- Once endometrial Ca excluded no need for further treatment of bleeding
- Endometrial ablation not recommended for PMW – can be difficult to assess for Ca after procedure