# Abnormal Uterine Bleeding (AUB)

**Premenopausal**: Any variation from the normal menstrual cycle, & includes changes in regularity & frequency of menses, duration of flow, or amount of blood loss during or between regular menstrual periods.

**Postmenopausal**: spontaneous or unexpected uterine bleeding that occurs >1 year after the last menstrual period. Important to rule out endometrial carcinoma!

## Goals of Treatment

1. Manage underlying medical condition contributing to AUB.
2. If anemia present - start iron supplementation (see below).
3. Manage AUB - restore predictability of menses or stop it entirely.
4. Encourage patient to achieve & maintain healthy active lifestyle.
5. Ensure activities of daily living (e.g. work, social) are achievable.

## FIGO & SOGC Classification of AUB

**Premenopausal**: Any variation from the normal menstrual cycle, & includes changes in regularity & frequency of menses, duration of flow, or amount of blood loss during or between regular menstrual periods.

1. Blood loss 1-25% of menstrual flow
2. Blood loss >25% of menstrual flow

**Postmenopausal**: spontaneous or unexpected uterine bleeding that occurs >1 year after the last menstrual period. Important to rule out endometrial carcinoma!

1. Blood loss 1-25% of menstrual flow
2. Blood loss >25% of menstrual flow

## Treatment Considerations

### Medical tx
- should be first line once malignancy & pelvic pathology have been ruled out due to invasiveness & ↑ risk unless:
  - Failure to respond to, or inability to utilize medical therapy (due to AE/CI); significant anemia
  - Best to take on empty stomach (or HS)
  - Elemental iron (Fe++) 180-200mg/day e.g. Ferrous sulphate 900mg multi-dose regimens (up to 3x/daily)
  - ↑ absorption & ↓ Fe++ (300mg=35mg Fe++)
  - Ferrous gluconate ↑ tolerability but ↓ Fe++ (300mg=35mg Fe++)
  - Recommend with Vit C >200-1000mg to ↑ absorption & ↓ absorption

### Surgical Options
- Endometrial ablation, hysteroscopic polypectomy, myomectomy, & hysterectomy (only definitive/curative treatment)

### Drug-Related Causes
- Anticoagulants, antiepileptics (e.g. phenytoin, valproic acid), antipsychotics (1st gen & risperidone), corticosteroids, herbal products (e.g. chasteberry,danshen, ginseng, ginkgo, motherwort, & soy), hormon al contraceptives, levodopa, long-term estrogen therapy, NSAIDs, SSRIs, tamoxifen, TCAs; recent hx of epidural steroid injection (<2 months).

### Drug-Related Causes
- Non-Structural (COEIN)
- Structural (PALM)

### Systemic Causes
- Inherited Bleeding Disorders: if typical treatments fail, consider desmopressin or factor replacement (consult hematologist)

### Acute Bleeding Treatment
- IV estrogen, IV tranexamic acid, or OCs/progestins at high doses or in multi-dose regimens (up to 3x/daily)
- Dilatation & curettage or ablation considered in urgent situations
- Preserve hysterectomy as last resort due to ↑ morbidity with acute anemia & resulting impaired healing, further bleeding, & infection
- If patient presents with stroke (due to anemia), consider leuprolide acetate to manage bleeding until therapeutic plan determined

### Evidence suggests LNG-IUS superior to non-surgical treatment methods
- Adolescents: all else being equal, patient preference toward OCS and NSAIDs
- Pre-Menopausal Adult: higher suspicion for disease-related causes of AUB; patient preference toward LNG-IUS.

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**FIGO & SOGC Classification of AUB**

<table>
<thead>
<tr>
<th>Abnormal Uterine Bleeding</th>
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</tr>
</thead>
<tbody>
<tr>
<td>structural (Palm)</td>
<td>Ovarian Surgical</td>
</tr>
<tr>
<td>Non-structural (COEIN)</td>
<td>Coagulopathy (AUB-C)</td>
</tr>
<tr>
<td>Polyp (AUB-P)</td>
<td>Ovarian Dysfunction (AUB-O)</td>
</tr>
<tr>
<td>Adenomyosis (AUB-A)</td>
<td>Lesymatos (AUB-L)</td>
</tr>
<tr>
<td>Malignancy/Hyperplasia (AUB-M)</td>
<td>Endometrial (AUB-E)</td>
</tr>
<tr>
<td>Iatrogenic (AUB-I)</td>
<td>Not Yet Specified (AUB-N)</td>
</tr>
</tbody>
</table>

* Inherited Bleeding Disorders: if typical treatments fail, consider desmopressin or factor replacement (consult hematologist)

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**TREATMENT OVERVIEW**

<table>
<thead>
<tr>
<th>Adolescent &amp; Premenopausal Adult</th>
<th>Perimenopausal AUB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further investigations or Tailor tx to cause</td>
<td>Further investigations or Tailor to cause (Consider Gynecologist consult)</td>
</tr>
<tr>
<td>Investigations Normal (Investigations should rule out pregnancy &amp; infection)</td>
<td>Investigations Normal (Investigations should rule out endometrial hyperplasia/carcinoma)</td>
</tr>
<tr>
<td>Proceed with 3-6 month trial of therapy (all non-hormonal options can be combined with hormonal options)</td>
<td>YES</td>
</tr>
<tr>
<td>Trasxamic Acid NSAID OCS LNG-IUS Progestin (21d)</td>
<td>YES</td>
</tr>
<tr>
<td>Progesterone OCS LNG-IUS Progestin (21d)</td>
<td>YES</td>
</tr>
<tr>
<td>Proceed with 3-6 month trial of therapy based on patient factors (all non-hormonal can be combined with hormonal)</td>
<td>YES</td>
</tr>
<tr>
<td>Trasxamic Acid NSAID OCS LNG-IUS Progestin (21d)</td>
<td>YES</td>
</tr>
<tr>
<td>Is treatment successful?</td>
<td>YES</td>
</tr>
<tr>
<td>Further Investigations or Tailor to cause (Consider Gynecologist consult)</td>
<td>YES</td>
</tr>
</tbody>
</table>

*Contraindications to combined OCS: see next page for drug comparison table; can be used until menopause if non-smokers & no additional cardiovascular risk factors (e.g. Hypertension, obesity, DM).
### Abnormal Uterine Bleeding: Drug Comparison Charts

**Kellie Towriss BSP © www.RxFiles.ca**

#### HORMONAL OPTIONS - regulate menstrual cycle, ↓ likelihood of unscheduled/prolonged & heavy bleeding episodes (see RxFiles pg. 125-127)

<table>
<thead>
<tr>
<th>Drug Comparison Chart</th>
<th>Place in Therapy / Evidence</th>
</tr>
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<tbody>
<tr>
<td>Protect endometrium from unopposed estrogen &amp; ↓ risk of hyperplasia/carcinoma with addition of progestin</td>
<td>&amp; women with AUB who desire relative contraindication</td>
</tr>
<tr>
<td>LNG-LUS 1.5mg/21</td>
<td>- Menstrual blood loss: ↓ by 86%[^6] &amp; 89%[^11], 20-80%[^7] amenorrheic (less effective than surgery for ↓ bleeding, similar QOL)</td>
</tr>
<tr>
<td>- Dysmenorrhea improves</td>
<td>- Other: most reliable in obese &amp; overweight women[^30], may be used in leiomyoma, adenomyosis, &amp; bleeding due to pelvic pain; efficacy for 3-5 years but greatest ↓ seen in first 3 months</td>
</tr>
<tr>
<td>- If difficult to insert in nulliparous women: misoprostol 400mcg x1 inserted vaginally 4hr prior to procedure (ensure pregnancy test negative!); insert during menses</td>
<td></td>
</tr>
<tr>
<td>Combined OCs: (may offer continuous use, without a pill-free interval)</td>
<td>- Initial dosing varies in practice (e.g. initial 1 tab BID-QID) &amp; duration (2-14d)</td>
</tr>
<tr>
<td>Menstrual blood loss: ↓ by 40-50%</td>
<td></td>
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<tr>
<td>Dysmenorrhea improves</td>
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<tr>
<td>Dysmenorrhea improves for up to 70% of patients</td>
<td></td>
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<tr>
<td>May consider initial loading dose (2x regular dose) on first day</td>
<td></td>
</tr>
<tr>
<td>Begin the day before menses for 3-5 days or until bleeding ceases[^17]</td>
<td></td>
</tr>
</tbody>
</table>

#### NON-STEROIDAL Anti-Inflammatory Agents (NSAIDs) - ↓ total prostaglandin production to promote uterine vasosconstriction & ↓ bleeding in AUB

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Indications</th>
<th>Dosing</th>
<th>Adverse Effects / Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>Naprosyn, Aleve, tabs, susp, supp</td>
<td>Initial 1000mg x 1, then 500mg BID</td>
<td>Gl: gastritis, dyspepsia, peptic ulcers, edema, phototoxic reaction, small bowel ulceration (unlikely significant in most patients since therapy only once a few days per month)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Advil, Motrin</td>
<td>Initial 1200mg x 1, then 600mg TID</td>
<td>Caution: Avoid in CKD stage 3 (CrCl &lt;40mL/min), stage 4, stage 5 (unless dialysis), &amp; transplant (not recommended when CrCl &lt;30mL/min)</td>
</tr>
<tr>
<td>Mefenamic Acid</td>
<td>Ponstan, Mefenamic</td>
<td>Initial 500mg TID</td>
<td>Hypersensitivity, severe renal disease, platelet or coagulation disorders, pre-existing gastritis, and PUD, CrCl&lt;30mL/min</td>
</tr>
</tbody>
</table>

#### ANTI-FIBRINOLYTICS - ↓ Plasminogen activator inhibitor, reversibly binds to plasminogen to ↓ local fibrin degradation (w/o changing coagulation)

<table>
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<th>Adverse Effects / Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tranexamic Acid</td>
<td>Lysteda, Cyclokapron, tabs, susp, sup</td>
<td>1g po QID during menses (74g po daily) OR Acute: 10mg/kg IV Q8H, CrCl 30-60mL/min: 1300mg daily x 5d, &lt;30mL/min: 650mg daily x 5d</td>
<td>N/V/D, headaches, leg cramps, elevated VTE risk</td>
</tr>
<tr>
<td>Danazol</td>
<td>Cyclofen, Cyproterone</td>
<td>100-400mg daily (generally used shorter-term, &lt;6 months)</td>
<td>Gl: hair growth, acne, muscle cramps, GI upset, irritability, androgenic effects (e.g. hair growth)</td>
</tr>
<tr>
<td>GnRH agonists</td>
<td>Luteal depot</td>
<td>3.75mg, 7.5mg, 11.25mg</td>
<td>Long-term use limited by AE</td>
</tr>
<tr>
<td>Goserelin</td>
<td>Zoladex</td>
<td>6.3mg SC monthly</td>
<td>Allergy, suspected pregnancy</td>
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#### OTHER AGENTS - induces endometrial atrophy through suppression of hypothalamic-pituitary-ovarian axis (hypoestrogenic)

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<tr>
<td>Mifepristone</td>
<td>Mifeprex</td>
<td>5mg PO</td>
<td>Controls bleeding related to uterine fibroids &amp; fast onset of amenorrhea (7-10 days)</td>
</tr>
<tr>
<td>Ulipristal</td>
<td>Mifepristone</td>
<td>5mg PO</td>
<td>Menstrual blood loss: 91% controlled 19% in placebo (noninferior &amp; more sustained effect than levonorgestrel; effect may persist up to 6 months)</td>
</tr>
<tr>
<td>Other</td>
<td>&lt; 24 weeks</td>
<td>- Menstrual blood loss ↓ by 86%[^6] &amp; 89%[^11], 20-80%[^7] amenorrheic (less effective than surgery for ↓ bleeding, similar QOL)</td>
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[^11]: Dysmenorrhea improves | |
[^17]: May consider initial loading dose (2x regular dose) on first day | |
[^18]: Begin the day before menses for 3-5 days or until bleeding ceases[^17] | |
Further investigations for Special Circumstances

Bleeding Disorders: ↑ suspicion when initial onset of menses is heavy & regular bleeding patterns or presents with suggestive sx: postpartum hemorrhage; surgery-related bleeding, & bleeding associated with dental procedures; or frequent bruising, epistaxis, and bleeding gums. Further investigations: platelet count, PTT, INR, von Willebrand factor, & ristocetin factor

Peri-menopausal: consider endometrial sampling first line due to ↑ risk of endometrial hyperplasia/carcinoma in patients >45yrs or <45 WITH hx of unopposed estrogen exposure, failed medical management, or persistent AUB

Uterine Fibroids & AUB Treatment

Uterine fibroids are commonly found in women in the middle to later reproductive years & are associated with symptoms such as heavy bleeding, menstrual pain, pressure in the lower abdomen, infertility, & recurrent miscarriages. Uterine fibroids are thought to be estrogen and progesterone dependent because they shrink after menopause. Traditionally treatment has been the surgical route (myomectomy or hysterectomy), but drug treatments are becoming more relevant:

Agents currently used for Uterine Fibroids

1. GnRH agonists: ↓ uterine fibroid size (by ≤50%) & ↓ uterine fibroid-related symptoms, but treatment restricted to 3-6 months due to hypoestrogenic AE & fibroids return to pretreatment size once agents are stopped

2. LNG-IUS MIRENA: ↓ menstrual blood loss related to uterine fibroids & ↑ hemoglobin in women with anemia, but is not beneficial for uterine regression

3. Ulipristal FIBRISTAL: selective progestrone receptor modulator; ↓ uterine fibroid volume (≤31% vs placebo ↑ 3%); controls bleeding & faster onset of amenorrhea (noninferior & more sustained effect than leuprolide acetate); no serious side effects

Agents in the Clinical Trial Pipeline for the indication of Uterine Fibroid Associated Abnormal Uterine Bleeding:

• Mifepristone MIFEPREX: competitively binds & antagonizes progesterone receptors; inconsistent evidence on effect of uterine size reduction (0 to 50%); ↑ endometrial hyperplasia with no atypia (unsure of clinical implications)

• Asoprisnil: selective progesterone receptor modulator with high receptor & tissue specificity; 25mg/day ↓ volume by ≤36%; ↓ bloating, pelvic pain, & uterine artery blood flow; minimal hypoestrogenic effects

• Telapristone PROELLEX: selective progesterone modulator; doses of 12.5, 25, & 50mg ↓ fibroid size by 10.6, 32.6, & 40.3% respectively (leuprolide acetate 32.6% & placebo 10.6% ↓)

• Aromatase inhibitors (letrozole, anastrozole, fadrozole): antiestrogen; ↓ fibroid size & symptoms (menstrual volume, duration of menstruation, & dysmenorrhea); no serious side effects reported

References:


Additional References:


Lethaby A, Hussain M, Rishworth JR, et al. Progestogen or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database Syst Rev. 2015 Apr 30;4:CD002126. The levonorgestrel-releasing intrauterine device (LNG IUS) is more effective than oral medication as a treatment for heavy menstrual bleeding (HMB). It is associated with a greater reduction in HMB, improved quality of life and appears to be more acceptable long term but is associated with more minor adverse effects than oral therapy. When compared to endometrial ablation, it is not clear whether the LNG IUS offers any benefit with regard to reduced HMB and satisfaction rates and quality of life measures were similar. Some minor adverse effects were more common with the LNG IUS but it appeared to be more cost effective than endometrial ablation techniques. The LNG IUS was less effective than hysterectomy in reducing HMB. Both treatments improved quality of life but the LNG IUS appeared more cost effective than hysterectomy for up to 10 years after treatment.


RxFiles – Abnormal Uterine Bleeding – Tx Chart

Developed by Kellie Towriss, BSP (Pharmacy Resident, Saskatoon Health Region (2013; last revised, June 2015)

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