Optimizing Management of Abnormal Uterine Bleeding

Malcolm G. Munro MD, FRCS(c), FACOG
Professor, Department of Obstetrics & Gynecology
David Geffen School of Medicine at UCLA
Director of Gynecologic Services
Kaiser Permanente, Los Angeles Medical Center
Los Angeles, CA, USA

- Impact of AUB on Women
  - Clinical, Economic, and Lifestyle
- Communicating about AUB
  - colleagues, literature, patients
- Pathogenesis of AUB
  - A different look at causality
- Investigation of women with AUB
  - What to do, when to do it
- Therapeutic options
- Final thoughts

The Cultural Context of Menstruation

The Affected Populations

Menarche
Menopause

Premenarche
Birth - 10

Reproductive
10 - 14
14 - 45

Perimenarche
Perimenopause
Postmenopause

Early
50 - 60

Late
60 - Death

What % of reproductive aged women experience heavy menstrual bleeding during their lifetime?

A. 5%
B. 10%
C. 20%
D. 30%
E. 50%

Prevalence of HMB

- 20% > 80 cc/month
- 5% (age 30-49) present for care each year
  - Royal College General Practitioners: Morbidity Statistics HMSO 1986
- 30% Affected by heavy uterine bleeding at some time in their life
  - Barnard K et al. J Women’s Health 2003;12:911-9
The Cultural Context of Menstruation

Impact of Heavy Menstrual Bleeding

Quality of Life

Women who have a heavier flow are 72% as likely to be working as are women who have a lighter or normal flow.

... work loss from increased blood flow is estimated to be $1692 annually per woman...

Optimizing Management of Abnormal Uterine Bleeding

- Impact of AUB on Women — Clinical, Economic, and Lifestyle
- Communicating about AUB — colleagues, literature, patients

Menorrhagia

DUB

Spotting

Hypermenorrhoea

AUB Nomenclature?

Polymenorrhea

Menometrorrhagia

Heavy Menstrual Bleeding

Oligomenorrhea
Is “Menorrhagia” a...

A. Symptom/sign?
B. Diagnosis?
C. Symptom/sign and a diagnosis?

Recommenations Regarding "Classical" Nomenclature
Could design, interpretation, and application of clinical investigation of AUB be aided with a universally accepted staging system?

Leiomyoma Subclassification System

- 0: No Structural Abnormality
- 1: Submucosal
- 2: Submucosal
- 3: Submucosal
- 4: Submucosal
- 5: Submucosal
- 6: Submucosal
- 7: Submucosal

Optimizing Management of Abnormal Uterine Bleeding

- Impact of AUB on Women
  - Clinical, Economic, and Lifestyle
  - Communicating about AUB
    - colleagues, literature, patients
- Pathogenesis of AUB
  - A different look at causality

Physiology of the Onset of Menstruation and Subsequent Endometrial Hemostasis

Systemic Physiology

Endometrial Physiology

- PG F2α
- ET-1
- PAI
- Factor Xa
- MMP
- PAs

- Estradiol
- Progesterone

Cycle Day 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

17-Estradiol
Progesterone

- PG F2α
- ET-1
- PAI
- Factor Xa
- MMP
- PAs

- Estradiol
- Progesterone

Cycle Day 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Pathogenesis of AUB

What do we know regarding the role of leiomyomas in the pathogenesis of AUB?

What differentiates the majority of women whose myomas are asymptomatic, from the minority whose symptoms are caused by their lesions?
Pathogenesis of AUB with Submucous Leiomyomas

How do myomas contribute to AUB?

Potential Mechanisms

- **Endometrial Surface Area**
  - Little evidence

- **Vascular Dysregulation**
  - Increased venous plexi
    - Sampson (Surg Gyn Obstet 1912;14:215-30)
    - Faulkner (Am J Obstet Gynecol 1945;47:185-97)

- **Mechanism(s) of Vascular Dysregulation**
  - Mechanical?
  - Growth factors?
    - bFGF, VEGF, HBEGF, PDGF, PTHrP, TGF-β, Prolactin

---

### Table: Distribution of Pathologies

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Submucosal</th>
<th>Other</th>
<th>Endometrial</th>
<th>Untyped</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyp</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenomyosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>Submucosal</td>
<td>Other</td>
<td>Endometrial</td>
<td>Untyped</td>
</tr>
<tr>
<td>Malignancy &amp; Hypertrophy</td>
<td>Not Classified</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

What is the prevalence of disorders of hemostasis (“coagulopathies”) in women with heavy menstrual bleeding (“menorrhagia”)?

A. 1%
B. 3%
C. 8%
D. 13%
E. 18%

---

### Table: Prevalence of von Willebrand Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Menstrual</th>
<th>Reproductive</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Willebrand disease</td>
<td>14.1 (62)</td>
<td>4.0 (23)</td>
</tr>
</tbody>
</table>

---

*A Survey of Gynecologists Concerning Menorrhagia: Perceptions of Bleeding Disorders as a Possible Cause*
Causes of Ovulatory Dysfunction

- Obesity
- Low Body Weight
- Weight Change
- Psychological Stress
- Elite Athletes
- Endocrinopathy
  - Hypothyroid
  - Hypotestosterone (e.g., PCOS)
  - Prolactin
- Pharmaceuticals
  - Tricyclics, phenothiazines
- Idiopathic

Pathogenesis of HMB
Endometrial Prostaglandins and Local Hemostasis

- There is less PGE2 in the endometrium of women with anovulatory DUB. No progesterone

Pathogenesis of HMB in Ovulatory Women
Endometrial Prostaglandins: Decreased Vasoconstrictors; Increased Vasodilators

- The PGE2/PGE ratio is inversely related to the amount of menstrual blood loss.

- The endometrium of menorrhagic women is more efficient at producing prostacyclin (PGI2)

Pathogenesis of HMB in Ovulatory Women
Enhanced Fibrinolysis
Plasminogen Activator (PA) and Inhibitor (PAI)

Caused by a local disorder of endometrial hemostasis – deficiencies or excesses of proteins that have an impact on coagulation

Pathogenesis of HMB in Ovulatory Women
Enhanced Fibrinolysis
Plasminogen Activator (PA) and Inhibitor (PAI)
Pathogenesis of HMB

Plasminogen Activator (PA) and Local Hemostasis
- Concentrations of tissue PA activity and antigen are significantly higher in women with DUB compared to normal women. 
- Tranexamic acid significantly reduces PA activity menstrual blood simultaneously reducing menstrual loss by 58%. 

Possible Iatrogenic Causes:

<table>
<thead>
<tr>
<th>Type</th>
<th>Systemic Pharmaceuticals</th>
<th>Medical Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulp</td>
<td>• Gonadal Steroids</td>
<td>• Intruterine Devices</td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>• Estrogens</td>
<td>• Inert</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>• Progestins</td>
<td>• Copper</td>
</tr>
<tr>
<td></td>
<td>• Testosterone</td>
<td>• Progestin</td>
</tr>
<tr>
<td></td>
<td>• Other</td>
<td>• Other</td>
</tr>
<tr>
<td>Malignancy &amp; Hyperplasia</td>
<td>Not Classified</td>
<td></td>
</tr>
</tbody>
</table>

Post LNG-IUS Endometrial Impact

- 17βHSD-2
- High Prevalence of BTB
- Immature, naked & dilated vessels
- Time since insertion (Months)

Arteriovenous Malformation (AVM)

- Included in “Net Classified”
  • Arteriovenous malformations
  • Endometritis
  • Other
If neurosurgeons treated the brain like many gynecologists treat the uterus, decapitation would be seen as an attractive surgical option.

...Identification of the full spectrum of therapeutic alternatives for women with chronic AUB requires a thorough evaluation of the uterus.

"70% of the hysterectomies were judged to be recommended inappropriately."

"The most common reasons...were lack of adequate diagnostic evaluation and failure to try alternative treatments."

“The cavity hasn’t been properly evaluated until you look.”

Separate the asymptomatic...from the ones that actually cause AUB.
Initial screening for an underlying disorder of hemostasis in patients with excessive menstrual bleeding should be by a structured history:

1. Heavy menstrual bleeding since menarche
2. One of the following:
   a. Post-partum hemorrhage
   b. Surgical related bleeding
   c. Bleeding associated with dental work
3. Two or more of the following symptoms:
   a. Bruising 1-2 times/month
   b. Epistaxis 1-2 times/month
   c. Frequent gum bleeding
   d. Family history of bleeding symptoms

A positive screen comprises any of the following (1) heavy bleeding since menarche, one from list (2) or two or more from list (3). Patients with a positive screen should be considered for further evaluation including consultation with a hematologist and/or testing of von Willebrand factor and Ristocetin cofactor.


In your office environment, which of the following tools do you have access to for evaluation of patients with AUB?

A. TVUS only
B. TVUS and SIS
C. Hysteroscopy only
D. TVUS and Hysteroscopy
E. TVUS, SIS, and Hysteroscopy
F. None of the above

Endometrial Hyperplasia/Neoplasia
Polyps
Submucosal Leiomyomas
Adenomyosis
Transvaginal ultrasound
Evaluation of Women with AUB
Evaluation of Endometrial Cavity Structure
1 Transvaginal ultrasound
2 Infusion sonography

Evaluation of Women with AUB
Evaluation of Endometrial Cavity Structure
1 Transvaginal ultrasound
2 Infusion sonography
3 Hysteroscopy

Optimizing Management of Abnormal Uterine Bleeding
- Impact of AUB on Women
  - Clinical, Economic, and Lifestyle
- Communicating about AUB
  - Colleagues, literature, patients
- Pathogenesis of AUB
  - A different look at causality
- Investigation of women with AUB
  - What to do, when to do it
- Therapeutic options

Therapy for:
Acute Nongestational AUB
Parenteral Conjugated Estrogens

Class I
N=32
CEE (Premarin®) 25 mg IV q 4 hours

Medical Management of Acute Nongestational AUB

Efficacy: Multidose OC vs Multidose MPA
Cessation of Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Evaluable Patients</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA</td>
<td>76% (n=17)</td>
<td>65% (n=20)</td>
</tr>
<tr>
<td>OCP</td>
<td>88% (n=16)</td>
<td>70% (n=20)</td>
</tr>
</tbody>
</table>

P = 0.656

Munro et al Obstet Gynecol 2006;108:924-9

Efficacy: Multidose OC vs Multidose MPA
Avoidance of Emergent Procedure

<table>
<thead>
<tr>
<th></th>
<th>Avoided Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA</td>
<td>100% (n=20)</td>
</tr>
<tr>
<td>OCP</td>
<td>95% (n=20)</td>
</tr>
</tbody>
</table>

NS

Munro et al Obstet Gynecol 2006;108:924-9

Therapeutic Strategies for AUB

<table>
<thead>
<tr>
<th>Feature</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>Antifibrinolitics, NSAIDS, GNRH Agonists, Gonadal Steroids, SPRMS</td>
</tr>
<tr>
<td>Local</td>
<td>LNG-IUS</td>
</tr>
<tr>
<td>Targeted</td>
<td>Myomectomy; Uterine Artery Embolization/Occlusion (UAE/O)</td>
</tr>
<tr>
<td>Procedural</td>
<td>Fertility Sparing or Enhancing Myomectomy; Uterine Artery Embolization/Occlusion (UAE/O)</td>
</tr>
<tr>
<td>Targeted</td>
<td>Myoma Ablation; Myomectomy; Endometrial Ablation (EA)</td>
</tr>
<tr>
<td>Non-targeted</td>
<td>Uterine Artery Occlusion/Embolization; Hysterectomy</td>
</tr>
<tr>
<td>Minimal Access</td>
<td>EA, Myoma Ablation, Endoscopic Myomectomy, LSH, LH, UAE/O</td>
</tr>
<tr>
<td>Laparotomic</td>
<td>Abdominal Hysterectomy</td>
</tr>
</tbody>
</table>

Therapy for:
Chronic Heavy Menstrual Bleeding
Therapy for HMB
Medical Therapy for HMB-E

- Antifibrinolytics
  - Fraser G, McCarron G. Avian N. Cukierman J. Meats Syst Rev (2) (2)
  - Cyclic Progestins
    - COX Inhibitors
      - Danazol
        - LNG-IUS

COCs
Fraser IS, McCarron G.
Aust NZJ Obstet Gynecol 1991;31:66-70

Cyclic Progestins
Lethaby et al. Cochrane Database Syst Rev 2007 Jan 23(1)

COX Inhibitors

Danazol

LNG-IUS

Treatment of HMB-C
Tranexamic Acid

- Synthetic amino acid, first introduced in Sweden in 1969.
  - Prevents fibrinolysis and breakdown of clot.
  - Available in all of the developed world… except the US

Tranexamic Acid

Levonorgestrel – Intrauterine System (LNG-IUS)
Mirena®

Crosignani et al. Obstet Gynecol 1997;90:257-63

Therapy for HMB
Progestin IUD vs Resectoscopic Resection for Idiopathic “Menorrhagia”

- Reduced Amen/Hypo Satisfaction
- 0 20 40 60 80 100
- IUD EA
- • RCT
- • N=35 per group
- • 12 Month FU

Crosignani et al. Obstet Gynecol 1997;90:257-63

Crosignani et al. Obstet Gynecol 1997;90:257-63
Endometrial Ablation
for:
Chronic HMB

Therapy for HMB
Nonresectoscopic Endometrial Ablation (NREA) Devices

TheraChoice (Contained Heated Water)

Hydrotamerblator (Free Heated Saline)

Novasure (electrical RF

Her Option (Cryonics)

MEA (Microwave)

Therapy for HMB
FDA-Approved NREA Devices
12-Month Clinical Outcomes

* Not reported in FDA RCT

Aberdeen Endometrial Ablation
Re-operation (Hysterectomy or Repeat EA)

STOP-DUB Endometrial Ablation
Cumulative Repeat Surgery (Hysterectomy)

Endometrial Ablation: KP Northern California
Re-operation (Hysterectomy) by Type of EA


N=3,681

Fig. 1. Probability of hysterectomy by endometrial ablation technique, life-table method. Log rank test, P<0.05.

...there are limitations to the size and type of uterine cavity that may be treated with NREA devices.

And they are not useful for women with HMB who wish to maintain fertility.

Radiofrequency non-resectoscopic endometrial ablation was first published in 1937, more than 25 years before the first description of resectoscopic endometrial ablation.
Therapy for HMB

% Satisfaction with Medical Rx vs EA for HMB
Cooper et al Br J Obstet Gynecol 1999;106:258-65

- Class I (RCT)
- N=173
- Aberdeen group
- Rx was medical or endometrial resection (ER)
- Outcomes: Change in SF-36 baseline to 24 mos

Current endometrial ablation technology does not predictably create amenorrhea, is often/usually limited with respect to the spectrum of configurations that can be treated.

Therapy for Leiomyoma-Related AUB

Medical vs Surgical; Fertility Sparing vs Loss of Fertility

<table>
<thead>
<tr>
<th></th>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertility Sparing/Enhancing</td>
<td>Gonadal Steroids</td>
<td>Myomectomy</td>
</tr>
<tr>
<td></td>
<td>SPRMs</td>
<td>Myoma ablation</td>
</tr>
<tr>
<td></td>
<td>GnRHa</td>
<td>UAE/O</td>
</tr>
<tr>
<td>Removes Fertility</td>
<td>-</td>
<td>Total Hysterectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supracervical Hysterectomy</td>
</tr>
</tbody>
</table>

Effect of Mifepristone for Symptomatic Leiomyomata on Quality of Life and Uterine Size
A Randomized Controlled Trial
Fiscella et al Obstet Gynecol 2006;108:1381-7

Table 1. Characteristics of Participants Randomized

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (Range)</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>41 (20-57)</td>
<td>41 (20-57)</td>
<td>41 (20-57)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30 (25-40)</td>
<td>30 (25-40)</td>
</tr>
<tr>
<td>Education</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian (43%)</td>
<td>Caucasian (43%)</td>
</tr>
<tr>
<td></td>
<td>African-American (12%)</td>
<td>African-American (12%)</td>
</tr>
</tbody>
</table>

Mifepristone vs Placebo Double Blind RCT
Fiscella et al Obstet Gynecol 2006;108:1381-7

5mg/dy X 26 weeks
**SPRMs**

Mifepristone vs Placebo Double Blind RCT
Fiscella et al Obstet Gynecol 2006;108:1381-7

**Leiomyoma Medical Therapy**

**Aromatase Inhibitors**

**The Effect of Anastrozole on Uterine Leiomyoma**


- Prospective (Class III)
- N=41
- Anastrazole 1 mg/day
- Three cycles of 28 days
- Volumetric measurement by MRI or TVS
- Mean 55.6% volume reduction

**Therapy for Leiomyoma-Related AUB**

<table>
<thead>
<tr>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonadal Steroids</td>
<td>Myomectomy</td>
</tr>
<tr>
<td>SPRMs</td>
<td>Myoma ablation</td>
</tr>
<tr>
<td>Aromatase Inhibitors</td>
<td>UAE/O</td>
</tr>
</tbody>
</table>

- Fertility Sparing/Enhancing
- Removes Fertility
- Removes Fertility
**Targeted Therapy for Leiomyoma-Associated AUB**

MR-Guided Focused Ultrasound

---

**Non-Targeted Therapy for Myoma-Associated AUB**

Uterine Artery Embolization

---

**Uterine Artery Embolization for Treatment of Leiomyomata**

(Obstet Gynecol 2008;111:22-33)

Long-Term Outcomes From the HIBROD Registry

Scott C. Goodart, MS, James R. Spirt, MS, Robert C. Winfield-Evich, MS, Eric Peterson, MS, MHA, Stephen Prost, MS, Sherry Li, MS, and Evan R. Marks, MS, for the HIBROD Registry Steering Committee and Core Site Investigators

- Symptom Scores
- UFS-QOL Scores

---

**UAB for Leiomyomas**

Laparoscopic Bipolar Electrodesiccation

- Liu et al
  Fertil Steril 2001;75:417-22
- N=87, 85 technically successful
- Cohort study (Class II-2)
- Menorrhagia, dysmenorrhea and/or urinary frequency
- Followup 10.2 months (7-12)

---

**UAB for Leiomyomas**

Laparoscopic Uterine Artery Occlusion by Bipolar Electrodesiccation

- Repeat Interventions
  - Hysterectomy 9.79%
  - Myomectomy 2.82%
  - Repeat UAE 1.83%

Original N = 2,112

---

**Non-Targeted Therapy for Leiomyoma-Associated AUB**

Laparoscopic Uterine Artery Occlusion by Bipolar Electrodesiccation
Therapy for Leiomyoma-Related AUB

<table>
<thead>
<tr>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertility Sparing/Enhancing</td>
<td></td>
</tr>
<tr>
<td>Gonadal Steroids</td>
<td>Myomectomy</td>
</tr>
<tr>
<td>SPRMs</td>
<td>Myoma ablation</td>
</tr>
<tr>
<td>GnRHa</td>
<td>UAE/O</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Removes Fertility</td>
<td>Total Hysterectomy</td>
</tr>
<tr>
<td></td>
<td>Supracervical Hysterectomy</td>
</tr>
</tbody>
</table>

Clinical Impact of AUB
(all benign indications)
Farquhar et al. Obstet Gynecol 2002;99:229-34

Clinical Impact of AUB
(all benign indications)
Munro, Unpublished – Source AHRQ National Inpatient Sample 2008

Clinical Impact of AUB
(all benign indications)

Hospital Episode Statistics for England:
Hysterectomy and hysteroscopic/non-hysteroscopic vaginal surgery
Optimizing Management of Abnormal Uterine Bleeding

- Impact of AUB on Women
  - Clinical, Economic, and Lifestyle
- Communicating about AUB
  - colleagues, literature, patients
- Pathogenesis of AUB
  - A different look at causality
- Investigation of women with AUB
  - What to do, when to do it
- Therapeutic options
- Final thoughts

Surgical Preferences (Northern England)
Sculpher et al. Health Expect 1998;1:96-105

Main reasons for patients to choose one particular type of treatment over another.

<table>
<thead>
<tr>
<th>Reason</th>
<th>IUD group</th>
<th>Abortion group</th>
<th>Hysterectomy group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IUD</td>
<td>0 (22)</td>
<td>21 (22)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>No hysterectomy</td>
<td></td>
<td>10 (10)</td>
<td></td>
</tr>
<tr>
<td>No oral contraceptives</td>
<td>4 (17)</td>
<td>12 (14)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Advice of the gynaecologist</td>
<td>1 (4)</td>
<td>13 (14)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Short or no absence</td>
<td>9 (39)</td>
<td>14 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Fast recovery</td>
<td>3 (12)</td>
<td>10 (10)</td>
<td>0</td>
</tr>
<tr>
<td>No complaints surgery</td>
<td>0 (0)</td>
<td>10 (10)</td>
<td>20 (75)</td>
</tr>
<tr>
<td>Fast return to work</td>
<td>0 (0)</td>
<td>6 (0)</td>
<td></td>
</tr>
<tr>
<td>No general anesthesia</td>
<td>9 (32)</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>No-seal</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>No affluence</td>
<td>3 (11)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Data are in (%)


FERTILITY AND STERILITY®
Vol. 82, No. 1, July 2004

Malcolm G. Munro MD, FRCS(c), FACOG
Professor, Department of Obstetrics & Gynecology
David Geffen School of Medicine at UCLA
Director of Gynecologic Services
Kaiser Permanente, Los Angeles Medical Center
Los Angeles, CA, USA