**APPENDIX 1. Risk Factors for Endometrial Hyperplasia and Carcinoma**

### Premenopausal women*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>5.8</td>
<td>1.1–28.6</td>
</tr>
<tr>
<td>Colorectal cancer (HPNCC/Lynch syndrome†)</td>
<td>5.0</td>
<td>1.3–19.1</td>
</tr>
<tr>
<td><strong>Obesity:</strong> Weight ≥ 90 kg</td>
<td>5.5</td>
<td>2.9–10.6</td>
</tr>
<tr>
<td>Infertility</td>
<td>3.6</td>
<td>1.3–9.9</td>
</tr>
<tr>
<td><strong>Age:</strong> ≥ 45 years</td>
<td>3.1</td>
<td>1.5–6.1</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>2.8</td>
<td>1.1–7.2</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval

* Independent risk factors, multivariate analysis (n=1,033)

† Lynch syndrome is another term for hereditary nonpolyposis colorectal cancer, an inherited condition that increases risk of colon, endometrial, and a number of other cancers. This is the most common of the genetic syndromes linked with increased risk of colon cancer (estimates of about 3% of all colon CA).

**Sources:**

### Postmenopausal women

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR/RR*</th>
<th>95% CI</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of endometrial cancer or colorectal cancer</td>
<td></td>
<td></td>
<td>Definite risk, but detailed information not available for postmenopausal women</td>
</tr>
<tr>
<td>Overweight: BMI ≥ 26 kg/m²</td>
<td>2.0</td>
<td>1.05–3.7</td>
<td>Epidemiologic studies consistently show that obesity increases risk</td>
</tr>
<tr>
<td>Obesity: BMI ≥ 35 kg/m²</td>
<td>4.4–4.7</td>
<td>3.12–7.07</td>
<td></td>
</tr>
<tr>
<td>Age: Per year older than 55 years</td>
<td>1.03</td>
<td>0.99–1.03</td>
<td>Risk steadily increases with age</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.2</td>
<td>1.09–4.6</td>
<td></td>
</tr>
<tr>
<td>Nulliparity</td>
<td>2.1</td>
<td>0.9–4.8</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen(1)</td>
<td></td>
<td></td>
<td>Treatment &gt; 5 years increases risk at least fourfold</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; *RR, rate ratio.

[Note: at prevalence rates of about 10%, these statistics produce essentially the same values]

**Sources:**
## APPENDIX 2. Potential Causes of Abnormal Uterine Bleeding by Reproductive Status

<table>
<thead>
<tr>
<th>Reproductive Status</th>
<th>Causes</th>
</tr>
</thead>
</table>
| Early postmenarche  | - Anovulatory cycles: related to immaturity of the hypothalamic-pituitary-ovarian axis  
- Hypothalamic suppression: stress, weight loss, heavy exercise, eating disorder  
- Bleeding diathesis  
- Pregnancy  
- Pelvic infection |
| Reproductive years  | - Pregnancy and pregnancy-related conditions  
- Structural disease: polyps, adenomyosis, leiomyoma/fibroids  
- Malignancy and hyperplasia/premalignant conditions  
- Coagulopathy/bleeding diathesis  
- Ovulatory dysfunction/anovulation  
- Endocrine dysfunction: polycystic ovary syndrome, thyroid dysfunction, pituitary adenoma  
- Pelvic infection  
- Systemic disease: renal, hepatic |
| Perimenopause       | - Anovulation  
- Structural disease: polyps, adenomyosis, leiomyoma/fibroids  
- Malignancy and premalignant lesions |
| Menopause           | - Atrophy  
- Malignancy and premalignant lesions  
- Structural disease: polyps, fibroids, adenomyosis |
| All ages            | - Medications: contraceptives, antidepressants, thyroid hormone replacement, anticoagulants, nonsteroidal anti-inflammatory, aspirin, antipsychotics, antiepileptics, tamoxifen, and oestrogen therapy  
- Herbal preparations: ginko, ginseng, motherwort, soy |

### Sources:
### APPENDIX 3. Stepwise Approach to Premenopausal Abnormal Uterine Bleeding (AUB)

#### Step 1 – Presentation/History
- Amount of blood loss, flooding, fatigue, pain, impact on lifestyle and activities
- Ovulatory or anovulatory cycles
- Sexual history
- Pregnancy: explore current possibility & desire for future pregnancy
- Psychosocial issues: especially stress, depression
- Family history: bleeding disorder, blood clots

#### Step 2 – Physical Examination
- Weight, Height, BMI, Pulse and Blood pressure
- Thyroid
- Skin: pallor, ecchymosis, petechiae, abdominal striae, acne, hirsutism, acanthosis nigricans
- Speculum examination: Cervical screening + swabs; friable cervix associated with infection or dysplasia
  - Reassess or refer if abnormal cervical screening test
- Pelvic/bimanual examination: detect genital tract pathology
  - If abnormal, consider transvaginal U/S
  - If fibroids or polyps, refer

#### Step 3 – Investigation
- Rule out pregnancy and related bleeding first
- FBC: consider ferritin
- TSH: if symptoms/signs suggest thyroid dysfunction
- Coagulopathy screen: if family history or bleeding dyscrasia
- Pelvic Ultrasound: transvaginal preferred
- Refer for endometrial biopsy: if increased risk of endometrial hyperplasia, atypia, carcinoma

**Approach to results (as advised by gynae team):**
- Hyperplasia without atypia: medroxyprogesterone acetate 10 mg, 5–90 days; repeat biopsy in 3–6 months
- Atypia/carcinoma: joint oncology and gynae team management

**Endometrial cancer risk factors**
- BMI > 40 or weight >90 kg
- Age ≥ 45
- Diabetes
- Anovulatory cycles/Polycystic ovary (PCOS)†
- Family history of endometrial or colon cancer
- Tamoxifen use

**† Note:** Long-term risk of endometrial hyperplasia or carcinoma exists with anovulatory cycles and PCOS. Protect endometrium with either hormonal contraceptives, Levonorgestrel-releasing intrauterine system or cyclical progestogens, progesterone 200-300 mg/d; norethisterone 15mg daily; or megestrol acetate 30 mg/d (Appendix 4).

#### Step 4 – Medical Therapy
**Ovulatory AUB**
- NSAIDs: start 24 hrs before and for duration of menses
- Tranexamic acid: antifibrinolytic that reduces blood loss; take 500-1500mg q 6-8 hours, day 1-4 only when bleeding
- Cyclical progesterogen norethisterone (15mg/day) or medroxyprogesterone (10 mg/day) x 21 days/month or Levonorgestrel-releasing intrauterine system

**Anovulatory AUB without atypia/cancer**
- Combination oral contraceptive: with ethinyl estradiol < 35 mcg, or Cyclical progesterone: (e.g., oral medroxyprogesterone 5-10 mg/day x 14 days/month) or Injectable medroxyprogesterone, or Levonorgestrel-releasing intrauterine system

#### Step 5 – Further Evaluations/Surgical Treatments if Failed Medical Therapy

**If not previously done consider:**
- Transvaginal ultrasound
- Endometrial biopsy
- Saline infusion sonohysterogram

**Also consider Gynaecological referral for:**
- Hysteroscopy
- Endometrial ablation
- Hysterectomy

**Note: D&C is no longer a treatment option for AUB since it has no long-term benefit** [Sources (1) and (2) below]

The management of acute bleeding in haemodynamically stable patients includes high-dose hormonal contraceptive (i.e., 35 mcg ethinyl estradiol) 2–4 pills/day x 7 days, then 1 pill/day x 14 days [Sources (1) and (5) below].


November 2012
### APPENDIX 4. Medications Commonly Used for Treatment of Abnormal Uterine Bleeding

<table>
<thead>
<tr>
<th>Medication/Agent</th>
<th>Dose</th>
<th>How it works</th>
<th>Side effects*</th>
<th>Contraindications</th>
<th>Approximate monthly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-steroidal anti-inflammatory drugs (NSAIDs)</strong></td>
<td>• Mefenamic acid 500 mg 6-8 hourly Naproxen 250-500 mg 6-12 hourly Ibuprofen 400 mg 4-6 hourly Diclofenac 50 mg tid</td>
<td>Reduces production of prostaglandin</td>
<td>Common: indigestion, diarrhea Uncommon: dizziness, headache, rashes Rare: worsening of asthma in sensitive individuals, ulcer with possible bleeding</td>
<td>Acute peptic ulcers or hx of ulcers, active IBD, hypersensitivity to NSAIDs Caution in patients with asthma, nasal polyps, renal disease, liver disease, CHF, HTN</td>
<td>Varies depending on type and brand used and amount needed per month Ibuprofen available OTC</td>
</tr>
<tr>
<td><strong>Tranexamic acid</strong></td>
<td>500-1500 mg 6-8 hourly prn (Note: 6 gm is maximum daily dose)</td>
<td>Anti-fibrinolytic agent</td>
<td>Uncommon: indigestion, diarrhea, headache</td>
<td>History, risk or active thromboembolic disease (DVT, PE) Acquired colour vision disturbance</td>
<td>60 tabs cost £5.21</td>
</tr>
<tr>
<td><strong>Combined Oral Contraceptive Pill (CoCP)</strong></td>
<td>As per package</td>
<td>Prevents proliferation of endometrium</td>
<td>Common: mood change, headache, nausea, fluid retention/bloating, breast tenderness, weight gain, breakthrough bleeding Very rare: DVT, stroke, heart attack</td>
<td>Hx of active thromboembolic disorder, cerebrovascular disorder, CHD, DVT, acute liver disease, breast cancer, migraine with aura, undiagnosed abnormal vaginal bleeding, pregnancy, uncontrolled HTN, smoker &gt; 35 years old</td>
<td>3 cycle pack £1.89 to £25.18 depending on brand</td>
</tr>
<tr>
<td><strong>Progestogen: Oral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Norethisterone</td>
<td>21 days/month</td>
<td>Prevents proliferation of endometrium</td>
<td>Common: weight gain, bloating, breast tenderness, headaches, acne (but usually minor and transient) Uncommon: nausea, headaches Rare: depression</td>
<td>Undiagnosed vaginal bleeding/ breast disease (including CA), pregnancy, severe liver disease, depression</td>
<td>Norethisterone 5mg 30 tab pack £2.10</td>
</tr>
<tr>
<td>• Medroxy-progesterone</td>
<td>5-10 mg</td>
<td></td>
<td></td>
<td></td>
<td>Medroxy-progesterone 5 mg 10 tab pack = £1.23</td>
</tr>
<tr>
<td><em>Ovulatory AUB:</em></td>
<td>15-25 mg /month</td>
<td></td>
<td></td>
<td></td>
<td>Norethisterone oral contraceptive 0.35 mg 3 x28 tabs</td>
</tr>
<tr>
<td>• Oral medroxyprogesterone 5-10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Norethisterone 15 mg daily day 5-25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Oral medroxyprogesterone 5-10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 – 14 d /month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Norethisterone oral contraceptive 0.35 mg daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progestogen: Injectable</strong></td>
<td>Medroxy progestosterone</td>
<td>Prevents proliferation of endometrium</td>
<td>Common: weight gain, irregular bleeding, amenorrhea, bloating/ fluid retention, breast tenderness Less common: bone density loss</td>
<td>Same as for oral progestogens (above)</td>
<td>£6.01 per injection</td>
</tr>
<tr>
<td></td>
<td>150mg IM every 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Monitor BMD if use &gt; 2 years</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progestogen: Intrauterine</strong></td>
<td>Levonorgestrel releasing system (LNG-IUS)</td>
<td>Device which slowly releases progestogen to prevent proliferation of endometrium</td>
<td>Common: irregular breakthrough bleeding (may last for 6 months), Less common: amenorrhea Rare: uterine perforation, expulsion, progestogen side effects from systemic absorption</td>
<td>Pregnancy, PID, undiagnosed uterine bleeding, uterine abnormalities that distort cavity, uterine/cervical malignancy, acute liver disease, immunodeficiency, leukaemia</td>
<td>£88 per device equals about £1.47 per month</td>
</tr>
</tbody>
</table>

*Common=about 1 in 100 chance; uncommon=about 1 in 1000 chance; rare=about 1 in 10,000 chance; very rare=about 1 in 100,000 chance

**Sources:**
### APPENDIX 5. Stepwise approach to postmenopausal abnormal uterine bleeding (AUB)

#### Step 1 – Presentation/History

<table>
<thead>
<tr>
<th>Differential Diagnosis &amp; Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic vaginitis 59%</td>
</tr>
<tr>
<td>Hormonal effect 7%</td>
</tr>
<tr>
<td>Endometrial polyp 17%</td>
</tr>
<tr>
<td>Cervical cancer 2%</td>
</tr>
<tr>
<td>Endometrial hyperplasia 10%</td>
</tr>
<tr>
<td>Other 17%</td>
</tr>
<tr>
<td>Endometrial carcinoma 10%</td>
</tr>
<tr>
<td>Source: Karlsson 1995</td>
</tr>
</tbody>
</table>

- Amount/frequency of blood loss
- Medications causing bleeding: HRT, anticoagulants, aspirin, tamoxifen
- Risk factors for endometrial Ca: obesity, diabetes, family history of Ca, etc.

#### Step 2 – Physical Examination

- General examination:
  - Height, Weight, BMI
  - Stigmata of liver disease
  - Ecchymosis

- Cervical screening test if not current or history of abnormality

- Pelvic examination:
  - External genitalia
  - Atrophic/infectious vaginitis
  - Uterine size/contour

- Cervical swabs or urine for PCR testing if at risk

#### Step 3 – Investigation/Treatment Principles

**FBC**

**INR, PTT, bleeding time, von Willebrand screen** if evidence of coagulopathy (bruising, bleeding elsewhere)

**TSH** if symptoms or signs of thyroid disease

**Evaluate the endometrium/uterine cavity**

- Transvaginal U/S, endometrial biopsy or both initially to assess endometrium
- Base choice of first investigation on patient preference, availability and local guidelines

**Transvaginal U/S performed first**

- If endometrial thickness below cut-off* (≤ 3mm) and symptoms resolve » watch
- If endometrial thickness above cut-off* (> 3mm) or symptoms persist » need endometrial evaluation
- *See Info point 18 re cut-off controversy.

**Endometrial biopsy**

- Normal
  - Symptoms resolve
  - Follow up
- Unable to perform or **Inadequate sample**
  - Symptoms persist
  - Transvaginal U/S (If not performed already – see above)

- Hyperplasia without atypia
  - Treatment with a progestogen may be considered with repeat biopsy in 3–6 months

- Hyperplasia with atypia/carcinoma
  - Gynaecology and oncology team treatment

#### Step 4 – Medical Therapy after investigations

- Topical oestrogen therapy for vaginal atrophy: creams, tablets, vaginal ring
- If taking systemic HRT, adjust medications by trial and error after ruling out pathology
  - Increase oestrogen and/or decrease progesterone if endometrial thickness ≤ 5 mm
  - Decrease oestrogen and/or increase progesterone if endometrial thickness > 5 mm
  - Vary dosing schedule: cyclical vs continuous

#### Step 5 – Further Evaluations/Surgical Treatments

- Hysteroscopy
- Saline infusion sonohysterogram
- Removal of polyp
- Hysterectomy

**Sources:**


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