Abnormal Uterine Bleeding: An Age Based Approach

Shannon C. Scott DO, FACOFP, Erin Raney, PharmD, BCPS, BC-ADM, Heather Johnston, OMS-IV, OMM National Undergraduate Fellow™

I. Midwestern University - Arizona College of Osteopathic Medicine
2. Midwestern University - College of Pharmacy-Glendale

INTRODUCTION

Abnormal Uterine Bleeding (AUB) is the preferred terminology for heavy menstrual bleeding or intermenstrual bleeding. 1 As defined by the Menstrual Disorders Working Group of the International Federation of Gynecology and Obstetrics (FIGO) and endorsed by the American College of Obstetricians and Gynecologists (ACOG), AUB is acute or chronic “bleeding from the uterine corpus that is abnormal in regularity, volume, frequency, or duration and occurs in the absence of pregnancy.” 2 Using the acronym PALCOEIN, both groups support the division of AUB into a classification system based on etiologies “related to uterine structural abnormalities” and “unrelated to uterine structural abnormalities”: P- Polyp, A- Adenomyosis, L- Leiomyoma, M- Malignancy and hyperplasia, C- Coagulopathy, O- Ovulatory dysfunction, E- Endometrial, I- Iatrogenic, and N- Not otherwise classified. This system should be used to guide a thorough medical history and physical exam for each patient. 3,4

In the last 20 years, endometrial cancer incidence has increased by 40%. 5 Endometrial cancer risk factors for women under age 40 include nulliparity, hypertension, body mass index (BMI) greater than 30, irregular menstruation, and family history. 6 Endometrial cancer should be considered in any postmenopausal woman with AUB, particularly since the risk of endometrial cancer increases with age. Postmenopausal women who are not on hormone replacement therapy that experience AUB have a 10% risk of endometrial cancer. 7 Endometrial cancer risk factors can be divided into non-modifiable and modifiable (Table 1). 8

TABLE 1:

Endometrial Cancer Risk Factors

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The medical history is very important when considering AUB. It should include age of menarche, bleeding patterns, and severity of bleeding. The terms menorrhagia (menstrual blood loss ≥ 80mL) and metrorrhagia (intermenstrual bleeding) have been replaced with heavy menstrual bleeding (AUB/HMB) and intermenstrual bleeding (AUB/MB), respectively. Medical history should also include surgeries, medications, and symptoms of hemostatic disorders. The physical exam should include general physical and pelvic examination - external, speculum with pap or human papilloma virus (HPV) test based on age specific screening guidelines, 9 and bimanual exam. Laboratory testing includes a pregnancy test, complete blood count, targeted screening for bleeding disorders (if risk factors present), and thyroid function tests. In addition, testing for Chlamydia trachomatis should be considered. Recommendations for diagnostic imaging and endometrial tissue sampling are based on age and risk factors and will be discussed in separate sections. 10

This review will use case examples to focus on three age groups of women with AUB: ages 18-35, 35-50, and over 50. Consideration of the medical history, physical exam, and management of common bleeding conditions will be highlighted. Where appropriate, associated co-morbid conditions and the risks of endometrial cancer will be discussed.

CASE 1: YOUNG ADULT – AGE 18-35

A 22-year-old female presents with abnormal menses. For the past 3 years, she has had 2-3 periods per year and the last one was 6 months ago. Each bleeding episode is heavy with cramping for about 7 days. She does not smoke or take any medications, and denies any illicit drug use or any bleeding disorders. She was evaluated during pregnancy and denies any past or present reproductive issues. Women of reproductive age women, polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory ovarian dysfunction (AUB-O). Menstrual cycles are determined anovulatory (AUB-O) if they are greater than 35 days from the previous one. 11 Our patient also had last menses 6 months ago, which is considered anovulatory amenorrhea and brings into consideration polycystic ovarian syndrome. The diagnosis of PCOS has been debated by specialty societies and criteria agreement includes the presence of 2 out of the 3 categories: hyperandrogenism, chronic anovulation (oligo- or amenorrhea), and polycystic ovaries (one or both ovaries on ultrasound with 12 or more follicles measuring 2.9 mm in diameter or increased ovarian volume greater than 10cm3). 12 The Androgen Excess Society requires the presence of hyperandrogenism, either physical or chemical signs, whereas the Rotterdam criteria requires any 2 of the 3 criteria. In our case, she has 2 of 3 criteria with amenorrhea and hyperandrogenism (acne, hirsutism, elevated testosterone). A pelvic ultrasound is not indicated to make the diagnosis of PCOS.

Our patient also has metabolic syndrome, 3 out of 5 criteria needed: increased waist circumference greater than 35 inches, FBS greater than or equal to 100 mg/dL, HDL cholesterol less than or equal to 40 mg/dL, triglycerides greater than or equal to 150 mg/dL, and blood pressure greater than 130/80. 13 ACOG recommends a two-hour oral glucose tolerance test for diagnosis of insulin resistance in patients with PCOS. 14

Insulin resistance is directly linked to the pathology of PCOS. The mechanisms proposed include direct stimulation of ovarian androgenogenesis, reduction in sex hormone-binding globulin, and disruption of the hypothalamic-pituitary axis which lead to hyperandrogenism and ovulatory dysfunction. 15 Insulin resistance further contributes weight gain that perpetuates the anovulatory cycle of PCOS.

Other causes of hyperandrogenism were ruled out in this case. Our patient had a normal FSH, LH, TSH, and prolactin that rule out primary ovarian failure, thyroid disease, and prolactin disorders. Free testosterone is recommended over total testosterone in the diagnosis of androgen excess, but physical exam findings are considered equally diagnostic. A 17-hydroxyprogesterone level should be done to rule out congenital adrenal hyperplasia. Unless rapid virilization is present, DHEA is not recommended. Cushing syndrome is extremely rare and screening is not recommended unless other criteria are present. 16

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The causes of AUB in adolescents and young adults overlap in pathology. Adolescents (ages 13-18) AUB is commonly caused by anovulation and an immature hypothalamic-pituitary-ovarian axis.7 Unrelated to the age at first menses, 60–80% of cycles become regular (21-34 days apart) within three years after the start of menarche. Most patterns of irregular bleeding in adolescence are considered physiologic and benign. Adolescent obesity has also reported to play an increasing role in anovulatory cycles.8

Up to 20% of patients with heavy bleeding that occur within the first few menstrual cycles may have an associated coagulation disorder. Reported risk factors include bleeding during dental work, surgery-related bleeding, frequent bruising, epistaxis, and or bleeding gums with tooth brushing, and family history of bleeding. Laboratory testing for coagulation issues include partial thromboplastin time, prothrombin time, activated partial thromboplastin time, fibrinogen, von Willebrand factor antigen, ristocetin cofactor assay, factor VIII, serum iron, total iron binding capacity, ferritin, and liver function test. For any abnormal coagulation factor test, a hematology consultation should be considered.9

In young adults (19-39 years) the most common causes of all AUB include pregnancy, structural lesions, anovulatory cycles, menstrual contra-coception, and hyperplasia.7 Our patient had a negative pregnancy test, ultrasound, and medication history. In reproductive age women, polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory ovarian dysfunction (AUB-O). Menstrual cycles are determined anovulatory (AUB-O) if they are greater than 35 days from the previous one.9 Our patient also had last menses 6 months ago, which is considered anovulatory amenorrhea and brings into consideration polycystic ovarian syndrome (PCOS).

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TABLE 2: Management of Hirsutism

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<tbody>
<tr>
<td>Laser Therapy</td>
<td>Well tolerated</td>
<td>Cost</td>
<td>None - but adding efflornithine to laser had better effects</td>
</tr>
<tr>
<td>Efflorescence HCl Facial Cream</td>
<td>Well tolerated, combined with laser therapy improves efficiency</td>
<td>Cost</td>
<td>Local stinging, burning, redness, rash</td>
</tr>
<tr>
<td>Spironolactone-aldosterone antagonist</td>
<td>BID dosing</td>
<td>Do not use in pregnancy</td>
<td>Hyperkalemia, Orthostatic hypotension</td>
</tr>
<tr>
<td>Flutamide-androgen receptor antagonist</td>
<td>Combined with lifestyle/ metformin add-on effects</td>
<td>Do not use in pregnancy</td>
<td>Dry skin, Hepatitis (rare)</td>
</tr>
<tr>
<td>Finasteride - 5-alpha reductase inhibitor</td>
<td>Better tolerated than other DHT blockers</td>
<td>Do not use in pregnancy</td>
<td>Rare</td>
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<td>Metformin</td>
<td>Cost</td>
<td>Results vary</td>
<td>Glutopen, diarrhea</td>
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**Hirsutism**

Hirsutism involves substantial growth of terminal hairs over the chin, neck, lower face, and chest. This hair growth typically has gradual onset and worsens with weight gain. Any patient with a rapid onset of hirsutism and atrophy of body hair should be evaluated for an androgen secreting tumor. Management of hirsutism is discussed in Table 2.13

The further management of PCOS is achieved with hormonal contraception, either combined hormonal contraception (CHC) or progestin-only derivatives. The levonorgestrel-releasing intrauterine system is also acceptable. There have been no studies suggesting that one hormonal contraceptive is superior to another. Progestin-only therapy may include side effects of irregular bleeding. Contraindications and tolerability of various hormonal contraceptives is further discussed in Case 2. According to the AACE, the optimal number of induced cycles per year have not been determined.

A large Australian retrospective study by Hart and Doherty in 2015 determined that PCOS increases the risk of many conditions. These include obesity, endometrial cancer, mortality, adult-onset diabetes, hypertension, ischemic heart disease, asthma, and mood disorders. Other studies have discussed an increased risk of sleep apnea.10 In addition to screening our patient for these co-morbid conditions, follow up monitoring of weight loss, insulin resistance, and cholesterol is recommended.

**CASE 2: ADULT – AGES 35-50**

A 46-year-old woman presents to clinic with complaints of irregular menstrual bleeding. She states that over the past year, her menstrual cycles are ranging from 20 to 36 days. Before that time, her cycles were regular and lasted around 27 days. She also reports heavier menstrual bleeding, with a length of 7 to 9 days. She reports no other complaints, such as hot flashes or sleep disturbances. She has a history of hypertension. Her last period was 2 months ago. Her partner is a non-smoker, and is currently sexually active with one partner for 6 months and uses condoms for contraception. She predicts a family history of breast cancer. The age of her grandmother was 73 to 34 without adverse effects. She reports a BMI of 27 kg/m2 and blood pressure of 118/70 mmHg. Her pelvic exam is normal and her TSH and CBC are within normal limits. A urine pregnancy test is negative. An endometrial biopsy is negative and transvaginal ultrasound shows no structural abnormalities.

Nearby women are experiencing changes in menstrual bleeding patterns for 4 to 8 years preceding menopause due to declining ovarian function.13 Although common, complaints of abnormal uterine bleeding during this time must be fully evaluated to rule out other potential causes. The hormone imbalance between estrogen and progesterone that occurs during this time increases risk for endometrial hyperplasia or cancer. Uterine adenomyosis, thyroid disorders, and coagulopathies are additional examples of pathology associated with abnormal bleeding.

Transvaginal ultrasonography, hysteroscopy, and saline infusion hystography can facilitate the detection of anatomic pathology. Endometrial sampling is a key procedure in women with AUB who are 45 years or older. It is also indicated for women who are younger than 45 years if they have a history of unopposed estrogen exposure such as in PCOS, family history of hereditary nonpolyposis colorectal cancer or endometrial cancer or have persistent AUB that fails medical management. In addition to these studies, it is important to assess for iron deficiency anemia and to rule out pregnancy prior to considering treatment options.

The endometrial biopsy for our patient is negative and her normal CBC indicates no need for iron replacement. As anatomic causes are ruled out, the management of AUB-O is a primary concern. Our patient should focus on a woman’s individual concerns related to quality of life. While medical and surgical options exist, either hormonal or non-hormonal pharmacologic strategies are typically considered first-line.

**Hormonal options**

Hormonal contraceptives are a viable option for perimenopausal women who are sexually active. Combined hormonal contraceptives (CHCs), containing estrogen and progestin, regulate the menstrual cycle and reduce both the length and volume of menstrual bleeding. If acute management of bleeding is needed, a monophasic oral product containing 35 mcg of estrogen should be considered. If bleeding persists, an oral medroxyprogesterone may be given as 20 mg three times daily for 7 days. For chronic management, oral medroxyprogesterone acetate 10 mg daily is given for 10-14 days per month. An additional non-hormonal contraceptive option is a GnRH agonist, which down regulates the hypothalamic, pituitary, ovarian axis and leads to a “pseudomenopause.” These are generally not recommended as a first-line approach due to the lack of data in AUB-O and the risk for hot flashes and reduced bone density.19

**Non-hormonal options**

Women with contraindications to hormone products may be candidates for non-hormonal options. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid, naproxen, and ibuprofen are effective for the management of AUB through uterine vasooconstriction resulting from decreased prostaglandin synthesis.28 Because of the unique mechanism, NSAIDs can be used in conjunction or alone. Clonidine and other alpha-2 agonists, such as uroflavin, can be added as an adjuvant for hormonal contraceptives. Women with an aspirin/NSAID allergy, bleeding disorders or who are taking other anticoagulant or antiplatelet medications should avoid this option.
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**Progestin-only contraceptives**

Progestin-only contraceptives are often selected for women who are not candidates for estrogen. Unlike combined estrogen-progestin products that provide a regular withdrawal bleed, many women experience amenorrhea after months of progestin-only product use. Unfortunately, unpredictable spotting is common as they are initiated, with a gradual reduction in bleeding episodes over time. 15 There are four levonorgestrel IUDs available in the US. The 52 mg LNG-IUS (Mirena) has a FDA-approved indication for menorrhagia, and has been shown to reduce menstrual blood loss, with high acceptability. 16 The contraceptive subdermal implant provides contraception for up to 3 years and is associated with variable menstrual bleeding patterns, with more than half of women experiencing irregular bleeding or amenorrhea. 16-18 The depot medroxyprogesterone acetate injection, administered every 3 months, produces amenorrhea in the majority of women after 1 year of use. It also has been shown to improve hot flashes associated with perimenopause. However, its use is associated with decreased bone density, which is concerning as a woman approaches menopause. 19-21

**Non-hormonal options:**

Women with contraindications to hormone products may be candidates for non-hormonal options. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid, naproxen, and ibuprofen are effective for the management of AUB through uterine vasoconstriction resulting from decreased prostaglandin synthesis. 22 Because of the unique mechanism, NSAIDs can be used in conjunctive therapy that limit the bleeding phase. 22 The combined hormonal contraceptive is a viable option for women who are sexually active. Combined hormonal contraceptives (CHCs), containing estrogen and progestin, regulate the menstrual cycle and reduce both the length and volume of menstrual bleeding. 22 If acute management of bleeding is needed, a monophasic oral product containing 35 mcg of ethinyl estradiol may be administered every 3 months, produces amenorrhea in the majority of women after 1 year of use. It also has been shown to improve hot flashes associated with perimenopause. However, its use is associated with decreased bone density, which is concerning as a woman approaches menopause. 19-21

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Tranexamic acid is a fibrinolytic that reduces the volume of uterine bleeding, and is an option to manage acute bleeding in an oral dose of 1300 mg three times daily for 5 days. It can be used to manage chronic bleeding, although it does not address the underlying cause. Caution is advised due to its associated risk for VTE, which is exacerbated by concomitant use of estrogen-containing contraceptives.

Surgical options of endometrial ablation and hysterectomy are typically reserved for use in older women who fail in women who are not candidates for medical management.4,11

Our patient is sexually active and does not appear to have contraindications to estrogen or progestogen containing contraceptive products. She is not experiencing hot flashes, so a combined hormonal or progestin-only contraceptive may be used. The decision may be made based upon whether she would prefer a predictable withdrawal bleeding pattern, or a progestin-only method that would avoid amenorrhea for a few months of use. She is not a candidate for an NSAID due to her aspirin allergy, so this should be avoided as an adjunctive measure.

### CASE 3: OLDER ADULT, POST-MENOPAUSAL – AGE 50+

A 62-year-old, obese, nulligravid, female presents for a well- woman examination. She has never married and used condoms for contraception when she was sexually active. She has no significant past medical history and has not seen a doctor in the last 10 years. She believes that she has never had an abnormal pap smear. Her first menstrual period was at age 11 and she experienced menopause 6 years ago. She has never been on any hormone replacement therapy. She denies hot flushes or mood swings. The patient does mention however, an episode of vaginal spotting 2 weeks ago. The bleeding was managed by a pantiliner and lasted about 2 days. Her blood pressure and pulse are stable and BMI is 33kg/m². The recent results of an endovaginal ultrasound (TVUS) are indeterminate with poor visualization.

Any AUB in postmenopausal women should be further evaluated given the increased risk of endometrial cancer. Other non-malignant causes of postmenopausal bleeding include, but are not limited to: atrophic vaginitis, endometrial atrophy, fibroids, and genitourinary symptoms alone typically do not require additional screening.

Our patient had an initial TVUS reflecting poor visualization. Polyps. Our patient’s endometrial biopsy reflects hyperplasia with atypia, treatment with an oral progestin or LNG-IUD can be considered.23 Newer drugs in research have included metformin.24

Current recommendations consider systemic hormone therapy (HT) appropriate for management of common menopausal symptoms, including vasomotor and urogenital symptoms.25 Postmenopausal women with AUB who are currently using HT require unique consideration. It is well-established that unopposed systemic estrogen therapy in women with a uterus causes a substantial excess risk for endometrial cancer, which increases with time.26 27 Therefore, only women without a uterus should receive systemic estrogen alone for menopausal symptoms. All other women should receive a combination of estrogen and progestogen, which when given in a cyclic or continuous regimen, reduces the excess risk of endometrial cancer.27 Current research points to greater endometrial cancer risk reduction with a continuous use pattern.28 Daily continuous administration of estrogen plus progestogen is often associated with a variable and unpredictable bleeding pattern for several months, usually resulting in amenorrhea after that time. If the bleeding persists after 6 months, further endometrial evaluation is recommended. In contrast, the cyclic pattern (estrogen daily plus 12-14 days of progestogen per month) should allow a withdrawal bleed as the progestogen is stopped each cycle. Bleeding occurring outside this expected time should be evaluated.29

Women with a uterus who cannot tolerate a progestogen may be a candidate for estrogen plus bazedoxifene (a tissue-selective estrogen receptor modulator), which provides endometrial protection.30 Women who experience bothersome bleeding patterns on HT can consider non hormonal options for vasomotor symptoms, such as clonidine, gabapentin or pregabalin, or serotonin agonists.31 Notably, women without other endometrial cancer risk factors receiving local vaginal estrogen therapy for genitourinary symptoms alone typically do not require additional progestogen for endometrial protection. However, safety has not been studied beyond one year. Any uterine bleeding experienced by a woman receiving low dose, local vaginal estrogen should be investigated further.32

### SUMMARY

Clinical evaluation of abnormal uterine bleeding requires careful consideration of age-specific factors. Identification of the underlying causes, whether structural or otherwise, allows the clinician to determine whether a surgical or medical approach is most appropriate. All decisions must be individualized to a patient’s risk and reproductive plans.

### AUTHOR DISCLOSURES

No relevant financial affiliations

### REFERENCES


Therefore, only women without a uterus should have a high negative predictive value. TVUS will allow visualization of hyperplasia with atypia or carcinoma, definitive treatment includes a total hysterectomy for staging of the disease. If diagnosed early, endometrial carcinoma is usually confined to the uterus in 75% of cases. Early detection allows lower mortality rates and favorable prognoses. Non-surgical management may be considered in some patients who are younger and desire fertility or are not surgical candidates. If our patient’s endometrial biopsy reflects hyperplasia with atypia, treatment with an oral progestin or LNG-IUD can be considered. Newer drugs in research have included metformin.

Current recommendations consider systemic hormone therapy (HT) appropriate for management of common menopausal symptoms, including vasomotor and urogenital symptoms. Postmenopausal women with AUB who are currently using HT require unique consideration. It is well-established that unopposed systemic estrogen therapy in women with a uterus causes a substantial excess risk for endometrial cancer, which increases with time. Therefore, only women without a uterus should receive systemic estrogen alone for menopausal symptoms. All other women should receive a combination of estrogen and progestogen, when given in a cyclic or continuous regimen, reduces the excess risk of endometrial cancer. Current research points to greater endometrial cancer risk reduction with a continuous progestogen use pattern. Daily continuous administration of estrogen plus progestogen is often associated with a variable and unpredictable bleeding pattern for several months, usually resulting in an amenorrhea after the first cycle. If bleeding occurs after 6 months, further endometrial evaluation is recommended. In contrast, the cyclic pattern (estrogen daily plus 12-14 days of progestogen per month) should be used if a withdrawal bleed as the progestogen is stopped. In each cycle, bleeding occurring outside this expected time should be evaluated.

Women with a uterus who cannot tolerate a progestogen may be a candidate for estrogen plus bazedoxifene (a tissue-selective estrogen receptor modulator). Women who experience bothersome bleeding patterns on HT can also consider nonhormonal options for vasomotor symptoms, such as clonidine, gabapentin or pregabalin, or serotoninergic antidepressants. Notably, women without other endometrial cancer risk factors receiving local vaginal estrogen therapy for genitourinary symptoms alone typically do not require additional progestogen for endometrial protection. However, safety has not been studied beyond one year. Any uterine bleeding experienced by a woman receiving low dose, local vaginal estrogen should be investigated further.

CASE 3: OLDER ADULT, POST-MENOPAUSAL – AGE 50+
A 62-year-old, obese, nulligravid, female presents for a well- woman examination. She has never married and used condoms for contraception when she was sexually active. She has no significant past medical history and has not seen a doctor in the last 10 years. She believes that she has never had an abnormal pap smear. Her first menstrual period was at age 11 and she experienced menopause 6 years ago. She has never been on any hormone replacement therapy. She denies hot flashes or mood swings. The patient does mention however, an episode of vaginal spotting 2 weeks ago. The bleeding was managed by a pantiliner and lasted about 2 days. Her blood pressure and pulse are stable and BMI is 33kg/m

Our patient had an initial TVUS reflecting poor visualization. The next step in management includes an endometrial biopsy, hysteroscopy with dilation and curettage, or sonohysterography. The ACOG supports endometrial biopsy or transvaginal ultrasound (TVUS) for the initial evaluation of AUB in postmenopausal women. Either method is sufficient in most cases. The benefits of TVUS include less invasive, less expensive testing with a high negative predictive value. TVUS will allow visualization of structural polyps and fibroids. If the endometrial thickness on TVUS is less than 4 mm, the probability of endometrial cancer is 1.2%. Endometrial biopsy is not recommended. If the endometrial thickness is greater than 4 mm, endometrial biopsy, hysterectomy with dilation and curettage, or sonohysterography is advised. Classification of endometrial tissue and risk categories include both hyperplasia with atypia and hyperplasia without atypia. Hyperplasia with atypia has a greater risk for progression to carcinoma over 20 years, compared to hyperplasia without atypia. If our patient’s endometrial biopsy reflects hyperplasia with atypia or carcinoma, definitive treatment includes a total hysterectomy for staging of the disease. If diagnosed early, endometrial carcinoma is usually confined to the uterus in 75% of cases. Early detection allows lower mortality rates and favorable prognoses. Non-surgical management may be considered in some patients who are younger and desire fertility or are not surgical candidates. If our patient’s endometrial biopsy reflects hyperplasia with atypia, treatment with an oral progestin or LNG-IUD can be considered. Newer drugs in research have included metformin.

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