Evaluation and Management of Abnormal Uterine Bleeding in Premenopausal Women

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Abnormal uterine bleeding occurs in 9 to 14 percent of women between menarche and menopause, significantly impacting quality of life and imposing financial burden.¹ The etiologies and treatments for abnormal uterine bleeding over the reproductive years are best understood in the context of normal menstrual physiology. A normal cycle starts when pituitary follicle-stimulating hormone induces ovarian follicles to produce estrogen. Estrogen stimulates proliferation of the endometrium. A luteinizing hormone surge prompts ovulation; the resultant corpus luteum produces progesterone, inducing a secretory endometrium. In the absence of pregnancy, estrogen and progesterone levels decline, and withdrawal bleeding occurs 13 to 15 days postovulation.² Disruption of normal physiology, anatomic changes in the endometrium, or endometrial cancer may result in abnormal uterine bleeding. Genetic bleeding during childhood, uterine bleeding that requires emergent intervention, and postmenopausal uterine bleeding are also abnormal, but are beyond the scope of this article.

Terms associated with abnormal uterine bleeding are inconsistently defined in the literature, complicating the approach to evaluation and management.³ International experts are working to develop consensus on these definitions to improve evidence-based care.³ Abnormal uterine bleeding that occurs from adolescence through perimenopause can be broadly divided into two categories: anovulatory and ovulatory. Anovulatory bleeding is characterized by irregular or infrequent periods, with flow ranging from light to excessively heavy.⁴ Terms commonly associated with anovulatory bleeding include amenorrhea (absence of periods for more than three cycles), oligomenorrhea (menses occurring at intervals of more than 35 days), metrorrhagia...
Anovulatory Bleeding

At extremes of the reproductive years, irregular cycles resulting from anovulation can occur. Following menarche, the immature hypothalamic-pituitary-ovarian axis may result in anovulatory cycles for two to three years. Up to eight years before menopause, women may again have intermittent anovulatory cycles. During the rest of the reproductive years, however, recurrent irregular cycles may be caused by anovulation and are considered abnormal.

When ovulation does not occur, no corpus luteum forms to produce progesterone, leading to prolonged estrogenic stimulation of the endometrium, excessive proliferation, endometrial instability, and erratic bleeding. Approximately 6 to 10 percent of women with anovulation have underlying polycystic ovary syndrome. Uncontrolled diabetes mellitus, hypothyroidism, and hyperprolactinemia also may cause anovulation by interfering with the hypothalamic-pituitary-ovarian axis. Antiepileptics

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<td>14 percent of women with recurrent anovulatory cycles develop cancer or hyperplasia&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>Less than 1 percent of women develop cancer or hyperplasia if they have no more than one risk factor for endometrial cancer&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Test for bleeding disorder in adolescents&lt;sup&gt;4,6&lt;/sup&gt; and in women with one or more of the following risk factors: chronic anovulation&lt;sup&gt;6&lt;/sup&gt;, obesity&lt;sup&gt;12,13&lt;/sup&gt;, family history of bleeding disorder; menses lasting seven days or more with flooding or impairment of activities with most periods; history of treatment for anemia; history of excessive bleeding with tooth extraction, delivery or miscarriage, or surgery</td>
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<sup>TSH = thyroid-stimulating hormone. </sup>

<sup>*—Not usually needed in adolescents. </sup>

Information from references 2, 4, and 6 through 22.
(especially valproic acid [Depakene]) may cause weight gain, hyperandrogenism, and anovulation.\textsuperscript{10} Use of typical antipsychotics (e.g., haloperidol, chlorpromazine, thiothixene [Navane]) and some atypical antipsychotics (e.g., clozapine [Clozaril], risperidone [Risperdal]) may contribute to anovulation by raising prolactin levels.\textsuperscript{11}

Recurrent anovulation causes an increased risk of endometrial cancer.\textsuperscript{4,7,12} Endometrial carcinoma in adolescents is rare, but has been reported and should be considered if recurrent anovulation for two to three years or morbid obesity is present.\textsuperscript{23} About 14 percent of premenopausal women with recurrent anovulatory cycles develop endometrial cancer or its precursor, hyperplasia with atypia.\textsuperscript{7} Ten to 20 percent of endometrial cancers are diagnosed in premenopausal women.\textsuperscript{13,14} Women at highest risk of cancer have advanced age, obesity, nulliparity, infertility, diabetes, family history of colon cancer, long-term unopposed estrogen therapy, or a history of tamoxifen use.\textsuperscript{4,12-14} One study demonstrated the highest incidence of endometrial abnormality, ranging from hyperplasia without atypia to cancer, in premenopausal women 45 years or older with abnormal uterine bleeding (number needed to screen [\textit{NNS}] = 13), women weighing 198 lb (90 kg) or greater (\textit{NNS} = 8), or both (\textit{NNS} = 5).\textsuperscript{13} Hyperplasia without atypia is generally considered benign, with less than 5 percent of cases progressing to cancer.\textsuperscript{24,25} In contrast, 30 percent of cases of hyperplasia with atypia progress to cancer,\textsuperscript{24} and 42.6 percent of women with this pathology have undiagnosed, concurrent endometrial adenocarcinoma.\textsuperscript{26}

### EVALUATION

Patients with irregular cycles who should be evaluated include adolescents with consistently more than three months between cycles\textsuperscript{6} or those with irregular cycles for more than three years; women with suspected recurrent anovulatory cycles;\textsuperscript{4} and women who are likely perimenopausal and have increased volume or duration of bleeding over baseline, periods more often than every 21 days, intermenstrual spotting, or postcoital bleeding.\textsuperscript{27}

Initial evaluation of anovulatory uterine bleeding should include history, physical examination to look for obesity and hirsutism (manifestations of polycystic ovary syndrome),\textsuperscript{4,6} a pregnancy test, and measurement of thyroid-stimulating hormone\textsuperscript{4,8,9} and prolactin levels.\textsuperscript{4,9} ACOG recommends endometrial tissue assessment to rule out cancer in adolescents and in women younger than 35 years with prolonged unopposed estrogen stimulation, women 35 years or older with suspected anovulatory bleeding, and women unresponsive to medical therapy.\textsuperscript{4} Office endometrial biopsy is relatively inexpensive, convenient, and has a low risk of complications.\textsuperscript{20} Findings may include benign endometrium, simple or complex hyperplasia without atypia, hyperplasia with atypia, or endometrial adenocarcinoma.\textsuperscript{2,14} In premenopausal women, endometrial biopsy is 82.3 percent sensitive for detecting hyperplasia with atypia and 91 percent sensitive for detecting endometrial cancer; specificity is 98 percent for both\textsuperscript{29} (Table 2\textsuperscript{21,22,28-30}).

### Table 2. Imaging and Tissue Sampling for Detection of Endometrial Pathology in Premenopausal Women

<table>
<thead>
<tr>
<th>Test</th>
<th>Utility</th>
<th>Limitations or contraindications</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial biopsy</td>
<td>Readily available</td>
<td>Pregnancy, Active pelvic inflammatory disease, Clotting disorders, Cervical infection or pathology\textsuperscript{28}</td>
<td>91 percent sensitive and 98 percent specific for detecting cancer\textsuperscript{29} 82.3 percent sensitive and 98 percent specific for detecting hyperplasia with atypia\textsuperscript{29}</td>
</tr>
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<td>Office hysteroscopy</td>
<td>Direct visualization of the uterine cavity, Allows for directed biopsy at time of procedure</td>
<td>More expensive than transvaginal ultrasonography,\textsuperscript{21} Does not evaluate the myometrium or ovaries</td>
<td>94 percent sensitive and 89 percent specific for detecting intracavitary abnormality (data pooled from pre- and postmenopausal women)\textsuperscript{29}</td>
</tr>
<tr>
<td>Saline infusion sonohysterography</td>
<td>Has utility of transvaginal ultrasonography with improved capacity to diagnose endometrial abnormalities\textsuperscript{21,22}</td>
<td>More expensive than transvaginal ultrasonography, Limited availability compared with transvaginal ultrasonography</td>
<td>88 to 99 percent sensitive and 72 to 95 percent specific for detecting intracavitary abnormality in premenopausal women\textsuperscript{21,22}</td>
</tr>
<tr>
<td>Transvaginal ultrasonography</td>
<td>Detects uterine tumors, polyps, endometrial and myometrial abnormalities, Assesses ovaries</td>
<td>Less sensitive and specific than saline infusion sonohysterography</td>
<td>60 to 92 percent sensitive and 62 to 93 percent specific for diagnosing intracavitary abnormality in premenopausal women\textsuperscript{21,22}</td>
</tr>
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\textsuperscript{21,22,28-30}
Evaluation and Treatment of Anovulatory Abnormal Uterine Bleeding

Figure 1. Algorithm for the evaluation and treatment of anovulatory abnormal uterine bleeding.

Information from references 4, 8, 9, 12 through 14, and 31.

Women at low risk of endometrial cancer and women with benign endometrial histology who have continued irregular or excessive uterine bleeding despite treatment should undergo imaging to rule out concomitant structural changes.4,9 If no abnormalities are found, hysteroscopy should be considered.4 Figure 1 is an algorithm for the evaluation and treatment of anovulatory abnormal uterine bleeding.4,8,9,12-14,31

TREATMENT

There is little consensus on specific treatment regimens for anovulatory uterine bleeding.32 Pharmacologic treatment options are listed in Table 3.4,9,11,14,31,33-39 ACOG recommends treatment with combination oral contraceptives or cyclic progestin.4 Progestin therapy and oral contraceptives induce routine withdrawal bleeding, decrease the risk of hyperplasia or cancer, and correct any related excessive menstrual bleeding.4 Oral contraceptives containing 35 mcg or less of ethinyl estradiol are preferred.4 Cyclic oral medroxyprogesterone acetate (Provera) at a dosage of 10 mg per day for 10 to 14 days per month also is effective.9

Treatment options for women who have hyperplasia without atypia include cyclic medroxyprogesterone acetate at 10 mg per day for 14 days per month14 or Daily megesterol (Megace), 40 mg14 or Insert levonorgestrel-releasing intrauterine system (Mirena)31

After the initiation of treatment, endometrial biopsy should be repeated in three to six months to assure resolution of the hyperplasia.9,14 Because of the high rate of progression to cancer, women found to have hyperplasia with atypia should be referred to a gynecologist to review treatment options.14 Hysterectomy is the recommended treatment, but women desiring continued...
### Table 3. Pharmacologic Treatment of Abnormal Uterine Bleeding

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<th>Medication</th>
<th>Dosage</th>
<th>Cost of generic (brand)*</th>
<th>Comments</th>
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<tr>
<td><strong>Anovulatory bleeding</strong></td>
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| Combination oral contraceptives                 | ≤ 35 mcg of ethinyl estradiol monophasic or triphasic pills | NA ($9 to 92)           | Provides contraception
Contraindications include smokers older than 35 years, personal history or high risk of deep venous thrombosis or pulmonary embolism, multiple risk factors for arterial cardiovascular disease, history of breast cancer, and severe cirrhosis or liver cancer. |
| Medroxyprogesterone acetate (Provera)           | 10 mg per day for 10 to 14 days per month   | $13 ($38)                | Does not provide contraception
Caution in patients with severe hepatic dysfunction                                                        |
| Medroxyprogesterone acetate                     | 10 mg per day for 14 days per month         | $13 ($38)                | Does not provide contraception
Caution in patients with severe hepatic dysfunction                                                        |
| Megestrol (Megace)                              | 40 mg per day                               | $25 (NA as tablets)      | Does not provide contraception
Caution in patients with severe hepatic dysfunction                                                        |
| Levonorgestrel-releasing intrauterine system    | Releases 20 mcg per 24 hours                | NA ($562†)               | 96 percent regression rate for hyperplasia without atypia
Provides contraception for five years
May cause irregular bleeding or amenorrhea
Contraindications include breast cancer; uterine anomaly that distorts the cavity; acute pelvic or cervical infection; and severe cirrhosis or liver cancer. |

| **Endometrial hyperplasia without atypia**       |                                             |                          |                                                                                                               |
| Medroxyprogesterone acetate                     | 10 mg per day for 14 days per month         | $13 ($38)                | Does not provide contraception
Caution in patients with severe hepatic dysfunction                                                        |
| Megestrol (Megace)                              | 40 mg per day                               | $25 (NA as tablets)      | Does not provide contraception
Caution in patients with severe hepatic dysfunction                                                        |
| Levonorgestrel-releasing intrauterine system    | Releases 20 mcg per 24 hours                | NA ($562†)               | 96 percent regression rate for hyperplasia without atypia
Provides contraception for five years
May cause irregular bleeding or amenorrhea
Contraindications include breast cancer; uterine anomaly that distorts the cavity; acute pelvic or cervical infection; and severe cirrhosis or liver cancer. |

| **Ovulatory bleeding**                          |                                             |                          |                                                                                                               |
| Levonorgestrel-releasing intrauterine system    | Releases 20 mcg per 24 hours                | NA ($562†)               | FDA-approved for menorrhagia in 2009; see additional comments above                                            |
| Medroxyprogesterone acetate                     | 10 mg per day for 21 days per month         | $16 ($40)                | Does not provide contraception
Effective short-term therapy for decreasing heavy flow
Not tolerated as well long term as levonorgestrel-releasing intrauterine system
Caution in patients with severe hepatic dysfunction                                                        |
| Ibuprofen                                       | 600 to 1,200 mg per day, five days per month | $4 ($16)                 | Begin first day of menses and continue for five days or until menses ceases
Treats dysmenorrhea
Caution in patients with gastrointestinal risks                                                              |
| Naproxen sodium (Anaprox)                       | 550 to 1,100 mg per day, five days per month | $4 ($50)                 |                                                                                                               |
| Mefenamic acid (Ponstel)                        | 1,500 mg per day, five days per month       | $429 ($553)              |                                                                                                               |
| Tranexamic acid (Lysteda)                       | 650 mg; two tablets three times per day, five days per month | NA ($170)                | FDA-approved for menorrhagia in 2009
Begin first day of menses and continue for five days
Caution in patients with history or risk of thromboembolic or renal disease
Contraindicated if patient has active intravascular clotting or subarachnoid hemorrhage
Considerably more expensive than other available therapies                                                    |

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**FDA = U.S. Food and Drug Administration; NA = not available; NSAIDs = nonsteroidal anti-inflammatory drugs.**

*—Estimated retail price of one month’s treatment based on information obtained at http://www.drugstore.com (August 4, 2011). Generic price listed first; brand price listed in parentheses.

†—Estimated cost to the pharmacist based on average wholesale prices in Red Book. Montvale, N.J.: Medical Economics Data; 2010. Cost to the patient will be higher, depending on prescription filling fee and insertion fee.

Information from references 4, 9, 11, 14, 31, and 33 through 39.
Abnormal Uterine Bleeding

fertility may be candidates for progestin therapy and close follow-up. Women found to have adenocarcinoma should be referred to a gynecologic oncologist for hysterectomy and staging.

**Ovulatory Bleeding**

Ovulatory abnormal uterine bleeding, or menorrhagia, presents as bleeding that occurs at normal, regular intervals but that is excessive in volume or duration. Hypothyroidism, late-stage liver disease, or bleeding disorders may cause menorrhagia, as may structural changes, such as submucosal fibroids or endometrial polyps. Von Willebrand disease (vWD), the most common heritable bleeding disorder, is present in approximately 13 percent of women with menorrhagia. The prevalence is likely higher in adolescents presenting with excessive uterine bleeding. In contrast to women with anovulatory bleeding, women with ovulatory bleeding produce progesterone, slough the endometrium regularly, and have minimal risk of developing cancer. Approximately one-half of women with menorrhagia have no discernable cause.

**EVALUATION**

Initial evaluation of menorrhagia should include a pregnancy test, complete blood count, and measurement of thyroid-stimulating hormone level. The American Academy of Pediatrics and ACOG recommend evaluating adolescents with menorrhagia for possible bleeding disorders, specifically vWD. A woman with menorrhagia should be evaluated for a possible bleeding disorder if she has one or more of the following: a family history of bleeding disorder; menses lasting seven days or more with flooding or impairment of activities with most periods; a bleeding disorder; or a history of excessive uterine bleeding. Consequently, there are few data to support their effectiveness.

**TREATMENT**

The goals of treatment for menorrhagia are to reduce flow volume and to correct anemia. Hormonal and non-hormonal therapeutic options are available to patients. Oral contraceptives have been shown to reduce menorrhagia more effectively than oral progestins. The continuous progesterone release provided by the levonorgestrel-releasing intrauterine system reduces menorrhagia and hysterectomy at a significantly lower cost.

**Nonhormonal Therapies.** At scheduled pharmacologic doses, nonsteroidal anti-inflammatory drugs (NSAIDs) decrease prostaglandin levels, reducing menstrual bleeding. In one small study, naproxen sodium (Anaprox) and mefenamic acid (Ponstel) decreased flow volume by 46 and 47 percent, respectively. There is no evidence that one NSAID is more effective than another, but cost varies considerably.

Tranexamic acid (Lysteda), an antifibrinolytic that prevents activation of plasminogen, is FDA-approved.
for the treatment of menorrhagia. Two 650-mg tablets taken three times per day for the first five days of the cycle decreased bleeding significantly more than NSAIDs did.\textsuperscript{38} Although increased rates of thrombosis were initially a concern, long-term studies have not demonstrated this.\textsuperscript{38} Cost remains a limiting factor of tranexamic acid. It is likely most appropriate in women with bleeding disorders who desire fertility or have contraindications to oral contraceptives.

Surgery. Uterine polyps and leiomyomas, specifically submucosal fibroids, may cause menorrhagia. Available evidence suggests that hysteroscopic polypectomy reduces 75 to 100 percent of abnormal uterine bleeding symptoms in women with endometrial polyps.\textsuperscript{17} For menorrhagia associated with submucosal fibroids, surgical resection may allow women to maintain child-bearing capacity.\textsuperscript{16} Resection may normalize menses, but the clear long-term impact on reproduction is unknown.\textsuperscript{16} Alternatively, fibroids may be treated with uterine artery embolization, the percutaneous embolization of perifibroid vessels causing infarction of the fibroid.\textsuperscript{42} The effect of uterine artery embolization on future pregnancies also needs further study.\textsuperscript{42} Whether abnormal uterine bleeding caused by fibroids is treated with surgical resection or uterine artery embolization, approximately 20 percent of women subsequently

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**Evaluation and Treatment of Ovulatory Abnormal Uterine Bleeding**

Menstrual cycle regular but excessively heavy or more than seven days’ duration\textsuperscript{7}

Obtain history and perform physical examination to rule out systemic disease or enlarged uterus

Test for pregnancy, measure thyroid-stimulating hormone level,\textsuperscript{6,8,9} perform complete blood count\textsuperscript{9}

Adolescent\textsuperscript{4,6} or adult with positive screening results for possible bleeding disorder\textsuperscript{25} (Table 1)?

Evaluate for bleeding disorder in collaboration with hematologist\textsuperscript{6,15,18,19}

Perform imaging test for structural abnormality with transvaginal ultrasonography or saline infusion sonohysterography\textsuperscript{9,11,12} (if high risk of endometrial cancer [Table 1], consider endometrial biopsy in addition to imaging [Figure 1])

Submucosal fibroid

Endometrial polyp

Normal imaging results

Refer for possible fibroidectomy\textsuperscript{16} or Uterine artery embolization\textsuperscript{42}

Refer for polypectomy\textsuperscript{17}

Treat with 10 mg of medroxyprogesterone acetate (Provera) for 21 days per month for three to six months\textsuperscript{44} or Insert levonorgestrel-releasing intrauterine system (Mirena)\textsuperscript{39}

or Begin trial of nonsteroidal anti-inflammatory drug starting on first day of menses until menses ceases\textsuperscript{36,37}

or Tranexamic acid (Lysteda), two 650-mg tablets three times per day on days 1 through 5 of cycle\textsuperscript{42,43}

If excessive bleeding is unresponsive to three- to six-month trial of therapy, consider endometrial biopsy or referral for possible hysterectomy,\textsuperscript{4,9,32} endometrial ablation, or hysterectomy\textsuperscript{43}

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**Figure 2. Algorithm for the evaluation and treatment of ovulatory abnormal uterine bleeding.**

*Information from references 2, 4, 6, 8, 9, 15 through 22, 30, 34 through 39, 42, and 43.*
undergo a hysterectomy for recurrent abnormal uterine bleeding.16,42

If excessive uterine bleeding is unresponsive to medical intervention, endometrial ablation (the surgical destruction of the endometrium) may be considered.43 This intervention is considered permanent and not advised in women who desire continued fertility. By five years postablation, approximately one-third of women require a second operation.43

Hysterectomy is the definitive treatment for excessive uterine bleeding in women who no longer wish to conceive. Disadvantages include increased number of adverse effects, longer recovery time, and higher initial health care costs compared with uterine-sparing procedures.52,43 Hysterectomy also may be associated with ovarian failure nearly four years earlier than expected.47

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Air Force Medical Department or the U.S. Air Force at large. Address correspondence to Mary Gayle Sweet, MD, Virginia Tech Carilion School of Medicine, 1314 Peters Creek Rd., Roanoke, VA 24017 (e-mail: mgsweet@carilionclinic.org). Reprints are not available from the authors.

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