

# Evaluation and Management of Abnormal Uterine Bleeding in Premenopausal Women

MARY GAYLE SWEET, MD; TARIN A. SCHMIDT-DALTON, MD; and PATRICE M. WEISS, MD

Virginia Tech Carilion School of Medicine and Research Institute, Roanoke, Virginia

KEITH P. MADSEN, MD, Joint Base McGuire-Dix-Lakehurst, New Jersey

Up to 14 percent of women experience irregular or excessively heavy menstrual bleeding. This abnormal uterine bleeding generally can be divided into anovulatory and ovulatory patterns. Chronic anovulation can lead to irregular bleeding, prolonged unopposed estrogen stimulation of the endometrium, and increased risk of endometrial cancer. Causes include polycystic ovary syndrome, uncontrolled diabetes mellitus, thyroid dysfunction, hyperprolactinemia, and use of antipsychotics or antiepileptics. Women 35 years or older with recurrent anovulation, women younger than 35 years with risk factors for endometrial cancer, and women with excessive bleeding unresponsive to medical therapy should undergo endometrial biopsy. Treatment with combination oral contraceptives or progestins may regulate menstrual cycles. Histologic findings of hyperplasia without atypia may be treated with cyclic or continuous progestin. Women who have hyperplasia with atypia or adenocarcinoma should be referred to a gynecologist or gynecologic oncologist, respectively. Ovulatory abnormal uterine bleeding, or menorrhagia, may be caused by thyroid dysfunction, coagulation defects (most commonly von Willebrand disease), endometrial polyps, and submucosal fibroids. Transvaginal ultrasonography or saline infusion sonohysterography may be used to evaluate menorrhagia. The levonorgestrel-releasing intrauterine system is an effective treatment for menorrhagia. Oral progesterone for 21 days per month and nonsteroidal anti-inflammatory drugs are also effective. Tranexamic acid is approved by the U.S. Food and Drug Administration for the treatment of ovulatory bleeding, but is expensive. When clear structural causes are identified or medical management is ineffective, polypectomy, fibroidectomy, uterine artery embolization, and endometrial ablation may be considered. Hysterectomy is the most definitive treatment. (*Am Fam Physician*. 2012;85(1):35-43. Copyright © 2012 American Academy of Family Physicians.)

## ► Patient information:

A handout on abnormal uterine bleeding, written by the authors of this article, is provided on page 44.

Abnormal uterine bleeding occurs in 9 to 14 percent of women between menarche and menopause, significantly impacting quality of life and imposing financial burden.<sup>1</sup> 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.<sup>2</sup> Disruption of normal physiology, anatomic changes in the endometrium, or endometrial cancer may result in abnormal uterine bleeding. Genital

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.<sup>3</sup> International experts are working to develop consensus on these definitions to improve evidence-based care.<sup>3</sup> 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.<sup>4</sup> 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

**Table 1. Differential Diagnosis and Evaluation of Abnormal Uterine Bleeding**

Category	Characteristics	Differential diagnosis	Evaluation
Anovulatory	Irregular, often infrequent periods <sup>4</sup> Progesterone-deficient/estrogen-dominant state <sup>2</sup> Flow ranges from absent or minimal to excessive <sup>4</sup> 14 percent of women with recurrent anovulatory cycles develop cancer or hyperplasia <sup>7</sup>	Adolescence <sup>4,6</sup> Diabetes mellitus, uncontrolled <sup>6</sup> Eating disorder <sup>6</sup> Hyper- or hypothyroidism <sup>8,9</sup> Hyperprolactinemia <sup>4,9</sup> Medication effects Antiepileptics <sup>10</sup> Antipsychotics <sup>11</sup> Perimenopause <sup>4</sup> Polycystic ovary syndrome <sup>4,6</sup> Pregnancy <sup>4</sup>	Laboratory tests for pregnancy, TSH and prolactin levels <sup>4,8,9</sup> Endometrial biopsy in the following persons at-risk of cancer: Adolescents who are obese and have two to three years of untreated anovulatory bleeding <sup>4</sup> Women 35 years or younger with one or more of the following risk factors: chronic anovulation, <sup>4</sup> diabetes, <sup>12,13</sup> family history of colon cancer, <sup>12,13</sup> infertility, <sup>12,13</sup> nulliparity, <sup>12,13</sup> obesity, <sup>12,13</sup> tamoxifen use <sup>13,14</sup> Women older than 35 years with suspected anovulatory bleeding <sup>4</sup> Women with bleeding not responsive to medical therapy <sup>4</sup> Imaging (transvaginal ultrasonography or saline infusion sonohysterography) if bleeding does not respond to medical therapy <sup>9</sup>
Ovulatory	Regular intervals (every 24 to 35 days) with excessive bleeding or duration greater than seven days <sup>2</sup> Less than 1 percent of women develop cancer or hyperplasia if they have no more than one risk factor for endometrial cancer <sup>7</sup>	Bleeding disorder <sup>4,15</sup> Factor deficiency Leukemia Platelet disorder von Willebrand disease Hypothyroidism <sup>8,9</sup> Liver disease, advanced <sup>6</sup> Structural lesions Fibroids <sup>16</sup> Polyps <sup>17</sup>	Laboratory tests for pregnancy, complete blood count, <sup>9</sup> TSH level <sup>8,9</sup> Test for bleeding disorder in adolescents <sup>4,6</sup> and in women with one or more of the following risk factors <sup>19,20</sup> : 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 Imaging* (transvaginal ultrasonography or saline infusion sonohysterography) to rule out structural abnormality <sup>21,22</sup> Endometrial biopsy in women 35 years or younger with normal laboratory and imaging results and bleeding unresponsive to therapy, and in women older than 35 years with multiple risk factors for cancer <sup>4,12,13</sup>

TSH = thyroid-stimulating hormone.

\*—Not usually needed in adolescents.

Information from references 2, 4, and 6 through 22.

(menses at irregular intervals with excessive bleeding or lasting more than seven days), and dysfunctional uterine bleeding (anovulatory bleeding in which underlying etiologies have been ruled out).<sup>2</sup> The term dysfunctional uterine bleeding is sometimes used to encompass many other abnormal uterine bleeding patterns, so for clarity and consistency with the American College of Obstetricians and Gynecologists (ACOG), this article uses the term anovulatory abnormal uterine bleeding.<sup>4</sup>

In contrast to anovulatory patterns, ovulatory abnormal uterine bleeding (menorrhagia) occurs at regular intervals (every 24 to 35 days), but with excessive volume or duration of more than seven days.<sup>2</sup> Excessive menstrual bleeding is defined as the need to change menstrual products every one to two hours, passage of clots greater than 1 inch (2.54 cm), and/or “very heavy” periods as reported by the patient.<sup>5,6</sup> It is commonly associated with low ferritin levels.<sup>5</sup> *Table 1* summarizes the characteristics, differential diagnosis, and evaluation of anovulatory and ovulatory abnormal uterine bleeding.<sup>2,4,6-22</sup>

## 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.<sup>2,6</sup> Up to eight years before menopause, women may again have intermittent anovulatory cycles.<sup>2</sup> During the rest of the reproductive years, however, recurrent irregular cycles may be caused by anovulation and are considered abnormal.<sup>4</sup>

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.<sup>4</sup> Approximately 6 to 10 percent of women with anovulation have underlying polycystic ovary syndrome.<sup>4</sup> Uncontrolled diabetes mellitus,<sup>6</sup> hypo- or hyperthyroidism,<sup>8,9</sup> and hyperprolactinemia<sup>4</sup> also may cause anovulation by interfering with the hypothalamic-pituitary-ovarian axis.<sup>6</sup> Antiepileptics

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

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

Information from references 21, 22, and 28 through 30.

(especially valproic acid [Depakene]) may cause weight gain, hyperandrogenism, and anovulation.<sup>10</sup> 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.<sup>11</sup>

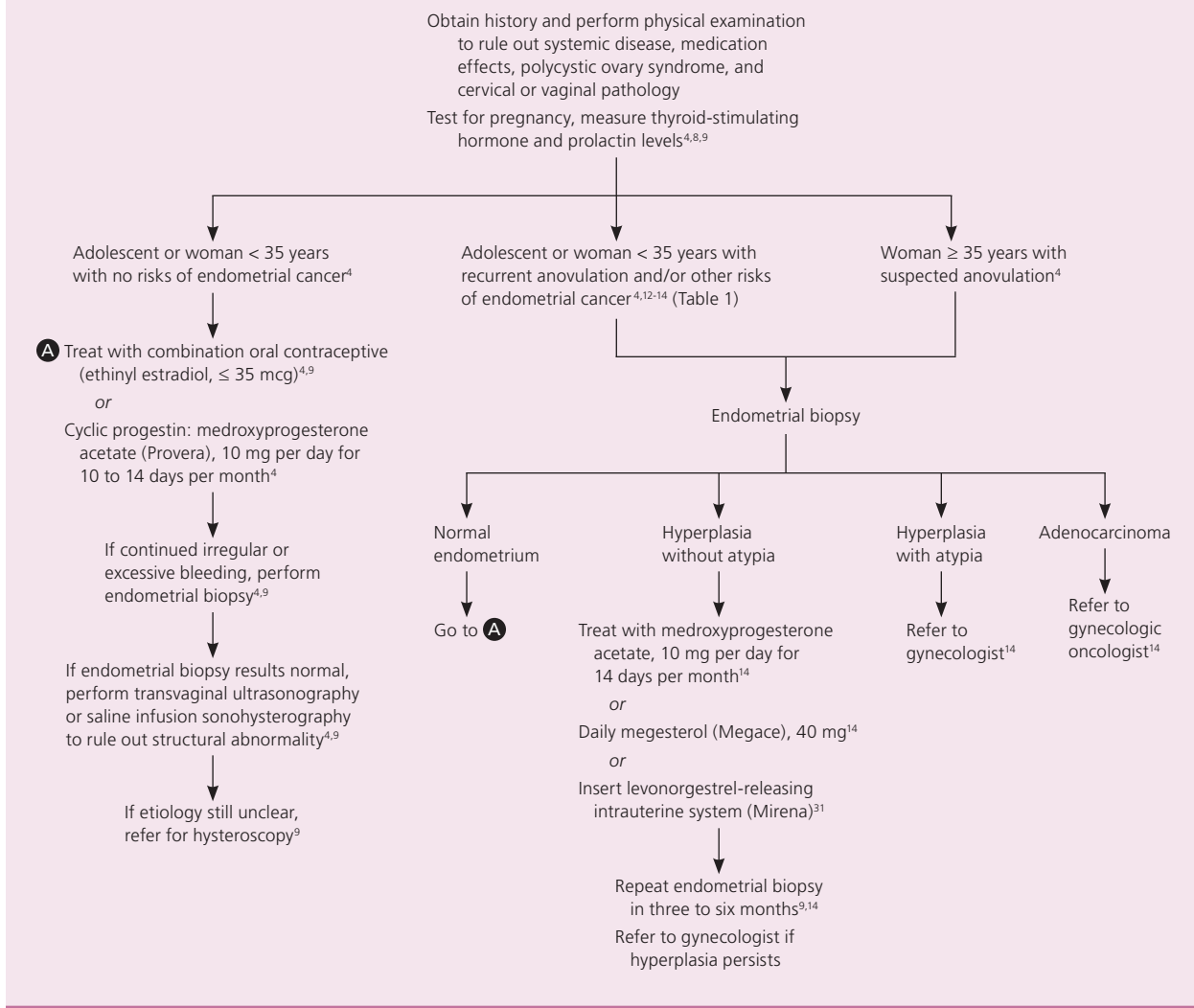
Recurrent anovulation causes an increased risk of endometrial cancer.<sup>4,7,12</sup> Endometrial carcinoma in adolescents is rare, but has been reported and should be considered if recurrent anovulation for two to three years or morbid obesity is present.<sup>23</sup> About 14 percent of premenopausal women with recurrent anovulatory cycles develop endometrial cancer or its precursor, hyperplasia with atypia.<sup>7</sup> Ten to 20 percent of endometrial cancers are diagnosed in premenopausal women.<sup>13,14</sup> 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.<sup>4,12-14</sup> 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 [NNS] = 13), women weighing 198 lb (90 kg) or greater (NNS = 8), or both (NNS = 5).<sup>13</sup> Hyperplasia without atypia is generally considered benign, with less than 5 percent of cases progressing to cancer.<sup>24,25</sup> In contrast, 30 percent of cases of hyperplasia with atypia progress to cancer,<sup>24</sup> and 42.6 percent of women with this pathology have undiagnosed, concurrent endometrial adenocarcinoma.<sup>26</sup>

## EVALUATION

Patients with irregular cycles who should be evaluated include adolescents with consistently more than three months between cycles<sup>6</sup> or those with irregular cycles for more than three years<sup>4</sup>; women with suspected recurrent anovulatory cycles<sup>4</sup>; 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.<sup>27</sup>

Initial evaluation of anovulatory uterine bleeding should include history, physical examination to look for obesity and hirsutism (manifestations of polycystic ovary syndrome),<sup>4,6</sup> a pregnancy test, and measurement of thyroid-stimulating hormone<sup>4,8,9</sup> and prolactin levels.<sup>4,9</sup> 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.<sup>4</sup> Office endometrial biopsy is relatively inexpensive, convenient, and has a low risk of complications.<sup>28</sup> Findings may include benign endometrium, simple or complex hyperplasia without atypia, hyperplasia with atypia, or endometrial adenocarcinoma.<sup>2,14</sup> 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<sup>29</sup> (Table 2<sup>21,22,28-30</sup>).

## 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.<sup>4,9</sup> If no abnormalities are found, hysteroscopy should be considered.<sup>4</sup> Figure 1 is an algorithm for the evaluation and treatment of anovulatory abnormal uterine bleeding.<sup>4,8,9,12-14,31</sup>

### TREATMENT

There is little consensus on specific treatment regimens for anovulatory uterine bleeding.<sup>32</sup> Pharmacologic treatment options are listed in Table 3.<sup>4,9,11,14,31,33-39</sup> ACOG recommends treatment with combination oral contraceptives or cyclic progestin.<sup>4</sup> Progestin therapy and oral contraceptives induce routine withdrawal bleeding, decrease the risk of hyperplasia or cancer, and correct

any related excessive menstrual bleeding.<sup>4</sup> Oral contraceptives containing 35 mcg or less of ethinyl estradiol are preferred.<sup>4</sup> Cyclic oral medroxyprogesterone acetate (Provera) at a dosage of 10 mg per day for 10 to 14 days per month also is effective.<sup>9</sup>

Treatment options for women who have hyperplasia without atypia include cyclic medroxyprogesterone acetate at 10 mg per day for 14 days per month, continuous megestrol (Megace) at 40 mg per day,<sup>14</sup> or the levonorgestrel-releasing intrauterine system (Mirena).<sup>31</sup> After the initiation of treatment, endometrial biopsy should be repeated in three to six months to assure resolution of the hyperplasia.<sup>9,14</sup> 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.<sup>14</sup> Hysterectomy is the recommended treatment, but women desiring continued

**Table 3. Pharmacologic Treatment of Abnormal Uterine Bleeding**

Medication	Dosage	Cost of generic (brand)*	Comments
<b>Anovulatory bleeding</b>			
Combination oral contraceptives <sup>4</sup>	≤ 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 <sup>33</sup>
Medroxyprogesterone acetate (Provera) <sup>9</sup>	10 mg per day for 10 to 14 days per month	\$13 (\$38)	Does not provide contraception Caution in patients with severe hepatic dysfunction
<b>Endometrial hyperplasia without atypia</b>			
Medroxyprogesterone acetate <sup>14</sup>	10 mg per day for 14 days per month	\$13 (\$38)	Does not provide contraception Caution in patients with severe hepatic dysfunction
Megestrol (Megace) <sup>11</sup>	40 mg per day	\$25 (NA as tablets)	Does not provide contraception Caution in patients with severe hepatic dysfunction
Levonorgestrel-releasing intrauterine system (Mirena) <sup>31</sup>	Releases 20 mcg per 24 hours	NA (\$562†)	96 percent regression rate for hyperplasia without atypia <sup>31</sup> 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 <sup>33</sup> More expensive initially, but similar to other therapies when averaged over five years
<b>Ovulatory bleeding</b>			
Levonorgestrel-releasing intrauterine system <sup>34,35</sup>	Releases 20 mcg per 24 hours	NA (\$562†)	FDA-approved for menorrhagia in 2009; see additional comments above
Medroxyprogesterone acetate <sup>34</sup>	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
<b>NSAIDs<sup>36,37</sup></b>			
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
Naproxen sodium (Anaprox)	550 to 1,100 mg per day, five days per month	\$4 (\$50)	Caution in patients with gastrointestinal risks
Mefenamic acid (Ponstel)	1,500 mg per day, five days per month	\$429 (\$553)	
Tranexamic acid (Lysteda) <sup>38,39</sup>	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 <sup>38,39</sup> 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

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.<sup>14</sup> Women found to have adenocarcinoma should be referred to a gynecologic oncologist for hysterectomy and staging.<sup>14</sup>

### 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.<sup>2</sup> Hypothyroidism,<sup>8,9</sup> late-stage liver disease,<sup>6</sup> or bleeding disorders<sup>4,6</sup> may cause menorrhagia, as may structural changes, such as submucosal fibroids or endometrial polyps.<sup>16,17</sup> Von Willebrand disease (vWD), the most common heritable bleeding disorder,<sup>19</sup> is present in approximately 13 percent of women with menorrhagia.<sup>18</sup> The prevalence is likely higher in adolescents presenting with excessive uterine bleeding.<sup>6,15</sup> In contrast to women with anovulatory bleeding, women with ovulatory bleeding produce progesterone, slough the endometrium regularly, and have minimal risk of developing cancer.<sup>7</sup> Approximately one-half of women with menorrhagia have no discernable cause.<sup>40</sup>

### EVALUATION

Initial evaluation of menorrhagia should include a pregnancy test, complete blood count,<sup>9</sup> and measurement of thyroid-stimulating hormone level.<sup>8,9</sup> The American Academy of Pediatrics and ACOG recommend evaluating adolescents with menorrhagia for possible bleeding disorders, specifically vWD.<sup>6,15</sup> 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 history of treatment for anemia; or a history of excessive bleeding with tooth extraction, delivery or miscarriage, or surgery.<sup>20</sup> Initial testing for bleeding disorders includes complete blood count (to assess for anemia, leukemia, and thrombocytopenia), and prothrombin and activated partial thromboplastin time (to assess for factor deficiencies).<sup>6,19</sup> The approach to further testing for bleeding disorders, specifically vWD, is varied, and collaboration with a hematologist is recommended.<sup>6,15,19,20</sup>

Although uncommon in adolescents,<sup>41</sup> uterine polyps and fibroids may underlie menorrhagia in women.<sup>16,17</sup> Transvaginal ultrasonography is used to evaluate the ovaries, uterus, and endometrium.<sup>21,22</sup> Saline infusion sonohysterography is the intrauterine infusion of saline during transvaginal ultrasonography that provides enhanced views of the endometrium.<sup>21</sup> In two small studies of premenopausal women, transvaginal

ultrasonography had 60 to 92 percent sensitivity and 62 to 93 percent specificity for diagnosing intracavitary lesions. In both studies, saline infusion sonohysterography improved sensitivity to 88 to 99 percent and specificity to 72 to 95 percent.<sup>21,22</sup>

If no etiology is found on ultrasonography, if bleeding is unresponsive to medical therapy, or if there are considerable risks of endometrial cancer, additional evaluation with endometrial biopsy<sup>4</sup> or direct visualization of the endometrium with hysteroscopy is recommended.<sup>30</sup> Hysteroscopy has a 94 percent sensitivity and 89 percent specificity for detecting intracavitary abnormalities.<sup>30</sup>

### 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 (*Table 3*<sup>4,9,11,14,31,33-39</sup>). *Figure 2* is an algorithm for the evaluation and treatment of ovulatory abnormal uterine bleeding.<sup>2,4,6,8,9,15-22,30,34-39,42,43</sup>

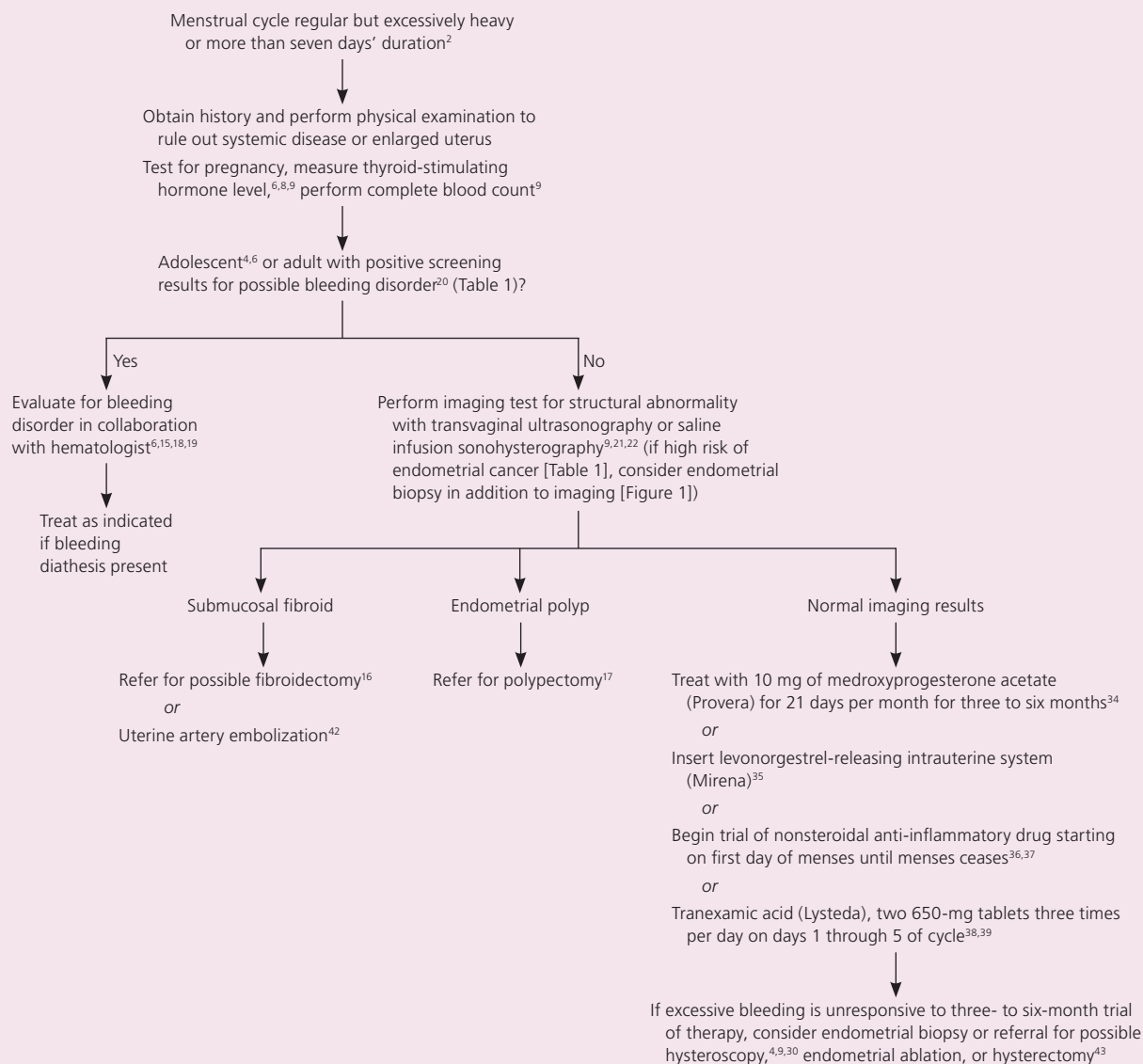
**Hormonal Therapies.** Progestins effectively decrease excessive menstrual bleeding. In contrast to the shorter course of oral progestin therapy used for anovulatory uterine bleeding, progestin therapy for menorrhagia needs to be given for 21 days per month to be effective.<sup>34</sup> The continuous progesterone release provided by the levonorgestrel-releasing intrauterine system reduces menorrhagia more effectively than oral progestins.<sup>35</sup> It is better tolerated than the 21-day oral regimen and has patient satisfaction scores similar to endometrial ablation and hysterectomy at a significantly lower cost.<sup>35,44</sup> The levonorgestrel-releasing intrauterine system is the only contraceptive approved by the U.S. Food and Drug Administration (FDA) for the treatment of menorrhagia.

Oral contraceptives have been shown to reduce menstrual flow volume, especially when used continuously,<sup>45</sup> but they have not been studied specifically in women with menorrhagia. Consequently, there are few data to support their effectiveness.<sup>46</sup> Oral contraceptives are, however, the treatment of choice in women with known vWD who also desire contraception.<sup>19</sup>

**Nonhormonal Therapies.** At scheduled pharmacologic doses, nonsteroidal anti-inflammatory drugs (NSAIDs) decrease prostaglandin levels, reducing menstrual bleeding.<sup>36</sup> In one small study, naproxen sodium (Anaprox) and mefenamic acid (Ponstel) decreased flow volume by 46 and 47 percent, respectively.<sup>37</sup> There is no evidence that one NSAID is more effective than another,<sup>36</sup> but cost varies considerably.

Tranexamic acid (Lysteda), an antifibrinolytic that prevents activation of plasminogen, is FDA-approved

## Evaluation and Treatment of Ovulatory Abnormal Uterine Bleeding



**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.

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.<sup>38</sup> Although increased rates of thrombosis were initially a concern, long-term studies have not demonstrated this.<sup>38</sup> 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.<sup>17</sup> For menorrhagia associated with submucosal fibroids, surgical resection may allow women to maintain child-bearing capacity.<sup>16</sup> Resection may normalize menses, but the clear long-term impact on reproduction is unknown.<sup>16</sup> Alternatively, fibroids may be treated with uterine artery embolization, the percutaneous embolization of perifibroid vessels causing infarction of the fibroid.<sup>42</sup> The effect of uterine artery embolization on future pregnancies also needs further study.<sup>42</sup> Whether abnormal uterine bleeding caused by fibroids is treated with surgical resection or uterine artery embolization, approximately 20 percent of women subsequently

## SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>	<i>Comments</i>
Adolescents with excessive uterine bleeding should be evaluated for bleeding disorders, such as von Willebrand disease.	C	4, 6, 15	Consensus guidelines
Saline infusion sonohysterography is more sensitive and specific for the detection of endometrial abnormalities than transvaginal ultrasonography.	C	21, 22	Meta-analysis and a small prospective comparison trial
The levonorgestrel-releasing intrauterine system (Mirena) is an effective treatment for menorrhagia, with patient satisfaction scores similar to endometrial ablation and hysterectomy.	A	35, 44	Cochrane review and randomized trial
NSAIDs are effective in reducing heavy menstrual blood flow. There is no evidence that one NSAID is more effective than another.	B	36	Cochrane review of nine small randomized controlled trials

NSAIDs = nonsteroidal anti-inflammatory drugs.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

undergo a hysterectomy for recurrent abnormal uterine bleeding.<sup>16,42</sup>

If excessive uterine bleeding is unresponsive to medical intervention, endometrial ablation (the surgical destruction of the endometrium) may be considered.<sup>43</sup> 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.<sup>43</sup>

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.<sup>42,43</sup> Hysterectomy also may be associated with ovarian failure nearly four years earlier than expected.<sup>47</sup>

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.

### The Authors

MARY GAYLE SWEET, MD, is an assistant professor of family medicine at the Virginia Tech Carilion School of Medicine and Research Institute, and is on the faculty at the Carilion Clinic Family Medicine Residency Program, both in Roanoke, Va.

TARIN A. SCHMIDT-DALTON, MD, is an assistant professor of family medicine at the Virginia Tech Carilion School of Medicine and Research Institute, and is on the faculty at the Carilion Clinic Family Medicine Residency Program.

PATRICE M. WEISS, MD, is a professor and chair of the Department of Obstetrics and Gynecology at the Virginia Tech Carilion School of Medicine and Research Institute, and is the chair of the Carilion Clinic Department of Obstetrics and Gynecology.

KEITH P. MADSEN, MD, is a physician with the 87th Medical Group family health clinic at Joint Base McGuire-Dix-Lakehurst, N.J. At the time the article was written, Dr. Madsen was chief resident at the Carilion Clinic Family Medicine Residency Program.

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](mailto:mgsweet@carilionclinic.org)). Reprints are not available from the authors.

Author disclosure: No relevant financial affiliations to disclose.

### REFERENCES

- Fraser IS, Langham S, Uhl-Hochgraeber K. Health-related quality of life and economic burden of abnormal uterine bleeding. *Expert Rev Obstet Gynecol*. 2009;4(2):179-189.
- Speroff L, Fritz MA. *Clinical Gynecologic Endocrinology and Infertility*. 7th ed. Philadelphia, Pa.: Lippincott Williams & Wilkins; 2005:402, 547, 549, 553-556, 560-561, 566, 569, 628-629, 808, 811.
- Fraser IS, Critchley HO, Munro MG, Broder M; Writing Group for this Menstrual Agreement Process. A process designed to lead to international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding [published correction appears in *Fertil Steril*. 2007;88(2):538]. *Fertil Steril*. 2007;87(3):466-476.
- ACOG Committee on Practice Bulletins—Gynecology. American College of Obstetricians and Gynecologists. ACOG practice bulletin: management of anovulatory bleeding. *Int J Gynaecol Obstet*. 2001;72(3):263-271.
- Warner PE, Critchley HO, Lumsden MA, Campbell-Brown M, Douglas A, Murray GD. Menorrhagia I: measured blood loss, clinical features, and outcome in women with heavy periods: a survey with follow-up data. *Am J Obstet Gynecol*. 2004;190(5):1216-1223.
- Diaz A, Laufer MR, Breech LL; American Academy of Pediatrics Committee on Adolescence, American College of Obstetricians and Gynecologists Committee on Adolescent Health Care. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Pediatrics*. 2006;118(5):2245-2250.
- Ash SJ, Farrell SA, Flowerdew G. Endometrial biopsy in DUB. *J Reprod Med*. 1996;41(12):892-896.
- Koutras DA. Disturbances of menstruation in thyroid disease. *Ann N Y Acad Sci*. 1997;816:280-284.
- Ely JW, Kennedy CM, Clark EC, Bowdler NC. Abnormal uterine bleeding: a management algorithm. *J Am Board Fam Med*. 2006;19(6):590-602.
- Morrell MJ, Hayes FJ, Sluss PM, et al. Hyperandrogenism, ovulatory dysfunction, and polycystic ovary syndrome with valproate versus lamotrigine. *Ann Neurol*. 2008;64(2):200-211.
- Madhusoodanan S, Parida S, Jimenez C. Hyperprolactinemia associated with psychotropics—a review. *Hum Psychopharmacol*. 2010;25(4):281-297.



12. Soliman PT, Oh JC, Schmeler KM, et al. Risk factors for young premenopausal women with endometrial cancer. *Obstet Gynecol.* 2005;105(3):575-580.
13. Farquhar CM, Lethaby A, Sowter M, Verry J, Baranyai J. An evaluation of risk factors for endometrial hyperplasia in premenopausal women with abnormal menstrual bleeding. *Am J Obstet Gynecol.* 1999;181(3):525-529.
14. Sorosky JL. Endometrial cancer. *Obstet Gynecol.* 2008;111(2 pt 1):436-447.
15. ACOG Committee on Gynecologic Practice. Committee Opinion: number 263, December 2001. von Willebrand's disease in gynecologic practice. *Obstet Gynecol.* 2001;98(6):1185-1186.
16. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. *Obstet Gynecol.* 2008;112(2 pt 1):387-400.
17. Nathani F, Clark TJ. Uterine polypectomy in the management of abnormal uterine bleeding: a systematic review. *J Minim Invasive Gynecol.* 2006;13(4):260-268.
18. Shankar M, Lee CA, Sabin CA, Economides DL, Kadir RA. von Willebrand disease in women with menorrhagia: a systematic review. *BJOG.* 2004;111(7):734-740.
19. James AH, Manco-Johnson MJ, Yawn BP, Dietrich JE, Nichols WL. von Willebrand disease: key points from the 2008 National Heart, Lung, and Blood Institute guidelines. *Obstet Gynecol.* 2009;114(3):674-678.
20. Philipp CS, Faiz A, Dowling NF, et al. Development of a screening tool for identifying women with menorrhagia for hemostatic evaluation. *Am J Obstet Gynecol.* 2008;198(2):163.e1-e8.
21. de Vries LD, Dijkhuizen FP, Mol BW, Brölmann HA, Moret E, Heintz AP. Comparison of transvaginal sonography, saline infusion sonography, and hysteroscopy in premenopausal women with abnormal uterine bleeding. *J Clin Ultrasound.* 2000;28(5):217-223.
22. Dueholm M, Forman A, Jensen ML, Laursen H, Kracht P. Transvaginal sonography combined with saline contrast sonohysterography in evaluating the uterine cavity in premenopausal patients with abnormal uterine bleeding. *Ultrasound Obstet Gynecol.* 2001;18(1):54-61.
23. Stovall DW, Anderson RJ, DeLeon FD. Endometrial adenocarcinoma in teenagers. *Adolesc Pediatr Gynecol.* 1989;2:157-159.
24. Lacey JV Jr, Chia VM. Endometrial hyperplasia and the risk of progression to carcinoma. *Maturitas.* 2009;63(1):39-44.
25. Lacey JV Jr, Ioffe OB, Ronnett BM, et al. Endometrial carcinoma risk among women diagnosed with endometrial hyperplasia: the 34-year experience in a large health plan. *Br J Cancer.* 2008;98(1):45-53.
26. Trimble CL, Kauderer J, Zaino R, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. *Cancer.* 2006;106(4):812-819.
27. Clinical challenges of perimenopause: consensus opinion of The North American Menopause Society. *Menopause.* 2000;7(1):5-13.
28. Gordon P. Videos in clinical medicine. Endometrial biopsy. *N Engl J Med.* 2009;361(26):e61.
29. Dijkhuizen FP, Mol BW, Brölmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. *Cancer.* 2000;89(8):1765-1772.
30. van Dongen H, de Kroon CD, Jacobi CE, Trimbos JB, Jansen FW. Diagnostic hysteroscopy in abnormal uterine bleeding: a systematic review and meta-analysis. *BJOG.* 2007;114(6):664-675.
31. Buttini MJ, Jordan SJ, Webb PM. The effect of the levonorgestrel releasing intrauterine system on endometrial hyperplasia: an Australian study and systematic review. *Aust NZ J Obstet Gynaecol.* 2009;49(3):316-322.
32. Hickey M, Higham J, Fraser IS. Progestogens versus oestrogens and progestogens for irregular uterine bleeding associated with anovulation. *Cochrane Database Syst Rev.* 2007;(4):CD001895.
33. Centers for Disease Control and Prevention (CDC). U.S. Medical Eligibility Criteria for Contraceptive Use, 2010. *MMWR Recomm Rep.* 2010;59(RR-4):1-86. <http://www.cdc.gov/mmwr/pdf/rr/rr59e0528.pdf>. Accessed August 24, 2011.
34. Lethaby A, Irvine GA, Cameron I. Cyclical progestogens for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2008;(1):CD001016.
35. Lethaby AE, Cooke I, Rees M. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2005;(4):CD002126.
36. Lethaby A, Augood C, Duckitt K, Farquhar C. Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2007;(4):CD000400.
37. Hall P, Maclachlan N, Thorn N, Nudd MW, Taylor CG, Garrioch DB. Control of menorrhagia by the cyclo-oxygenase inhibitors naproxen sodium and mefenamic acid. *Br J Obstet Gynaecol.* 1987;94(6):554-558.
38. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2000;(4):CD000249.
39. Lukes AS, Moore KA, Muse KN, et al. Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial. *Obstet Gynecol.* 2010;116(4):865-875.
40. Rees M. Menorrhagia. *Br Med J (Clin Res Ed).* 1987;294(6574):759-762.
41. Minjarez DA, Bradshaw KD. Abnormal uterine bleeding in adolescents. *Obstet Gynecol Clin North Am.* 2000;27(1):63-78.
42. Edwards RD, Moss JG, Lumsden MA, et al.; Committee of the Randomized Trial of Embolization versus Surgical Treatment for Fibroids. Uterine-artery embolization versus surgery for symptomatic uterine fibroids. *N Engl J Med.* 2007;356(4):360-370.
43. Dickersin K, Munro MG, Clark M, et al.; Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding (STOP-DUB) Research Group. Hysterectomy compared with endometrial ablation for dysfunctional uterine bleeding: a randomized controlled trial. *Obstet Gynecol.* 2007;110(6):1279-1289.
44. Hurskainen R, Teperi J, Rissanen P, et al. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow-up. *JAMA.* 2004;291(12):1456-1463.
45. Larsson G, Milsom I, Lindstedt G, Rybo G. The influence of a low-dose combined oral contraceptive on menstrual blood loss and iron status. *Contraception.* 1992;46(4):327-334.
46. Farquhar C, Brown J. Oral contraceptive pill for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2009;(4):CD000154.
47. Farquhar CM, Sadler L, Harvey SA, Stewart AW. The association of hysterectomy and menopause: a prospective cohort study. *BJOG.* 2005;112(7):956-962.