

# Abnormal uterine bleeding

## Taking the stress out of controlling the flow

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*Candace, a 49-year-old office administrator, comes to see you for her annual periodic health examination. She reports that her periods are becoming more irregular and unpredictable. Previously her menstrual cycle was 30 days, but during the past 6 months it has been 24 to 40 days. Her menses have been heavy since her second pregnancy 21 years ago and are getting worse. During the first 2 days of her period she has to change a super-size tampon and pad (used simultaneously) every 1 to 2 hours to prevent leaking onto her clothing; there is associated mild cramping but no appreciable blood clots. Her periods have become so bad that she often needs to take time off work during this time. She denies any spotting between periods or bleeding after coitus. She has occasional hot flashes with no other menopausal symptoms.*

*Candace recently started taking 25 mg/d of hydrochlorothiazide for essential hypertension. She has no other medical conditions. For menstrual cramps she takes 325 mg of acetaminophen every 6 hours when needed and 200 mg of ibuprofen once daily when needed. She has no known allergies. Surgical history includes a tonsillectomy as a child and tubal ligation. Her obstetric and gynecologic history includes a monogamous relationship with her husband and gravida 2, para 2—both were spontaneous vaginal deliveries with no complications or postpartum hemorrhage. Candace is a non-smoker and drinks alcohol only occasionally. Her family history is remarkable for hypertension in her mother; there is no family history of breast cancer or coagulopathies. Her mother had a hysterectomy at age 40 for fibroids.*

*Candace's physical examination reveals normal vital signs and a body mass index of 32 kg/m<sup>2</sup>. All physical examination findings are unremarkable except for a "bulky" uterus found during bimanual examination. Results of a recent Papanicolaou test were normal.*

*You perform an endometrial biopsy and order tests for complete blood count and thyroid-stimulating hormone levels, a urine test for chlamydia and gonorrhoea, and a pelvic ultrasound.*



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Abnormal uterine bleeding (AUB) is a condition that affects approximately 30% of women during their reproductive years.<sup>1</sup> It is a considerable health care burden for women and has a definite effect on quality of life. Health care practitioners deal with this problem frequently.<sup>2</sup>

Abnormal uterine bleeding has various definitions and classifications. It can be loosely defined as a variation from the normal menstrual cycle. The variation can be in regularity, frequency, duration of flow, or amount of blood loss. Often the bleeding is "heavy," which is "excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or material quality of life."<sup>3</sup> The terms *menorrhagia* and *metrorrhagia*, as well as other combinations, have become outdated.

Abnormal uterine bleeding might be classified as premenopausal, perimenopausal, or postmenopausal. In premenopausal and perimenopausal women, AUB can be further categorized as ovulatory and anovulatory. Ovulatory bleeding occurs at regular menstrual intervals and is typically associated with premenstrual symptoms and painful periods. Anovulatory bleeding is more common around menarche and menopause and is typified by heavy, irregular, and prolonged periods. There is a greater association of endometrial hyperplasia and cancer with anovulatory bleeding in perimenopausal and menopausal women.<sup>2</sup>

### Causes and treatment goals

There are many causes of AUB, including anatomic, systemic, and drug-related causes.<sup>4</sup> Once investigations have determined the cause and ruled out premalignant or malignant conditions, many of the treatment principles are the same. A detailed chart about the causes of and treatments for AUB is available from **CFPlus**.<sup>\*</sup> The overall treatment goals for AUB include managing contributing medical conditions, treating anemia if present, restoring predictability of bleeding or stopping menses, encouraging achievement of healthy body weight, and minimizing the effect of abnormal bleeding on a woman's daily activities.<sup>4</sup>

For our patient Candace, it is important to determine her expectations regarding her condition in order to develop a patient-centred management plan. Women often do research about treatment options and have

<sup>\*</sup>The RxFiles chart on **Abnormal Uterine Bleeding** is available at [www.cfp.ca](http://www.cfp.ca). Go to the full text of this article and click on **CFPlus** in the menu at the top right-hand side of the page.

spoken to friends and colleagues. Candace might be assuming that she will be offered a hysterectomy as her mother was in the past.

*Candace's investigation findings are normal. At the next visit, you review these findings and discuss treatment options.*

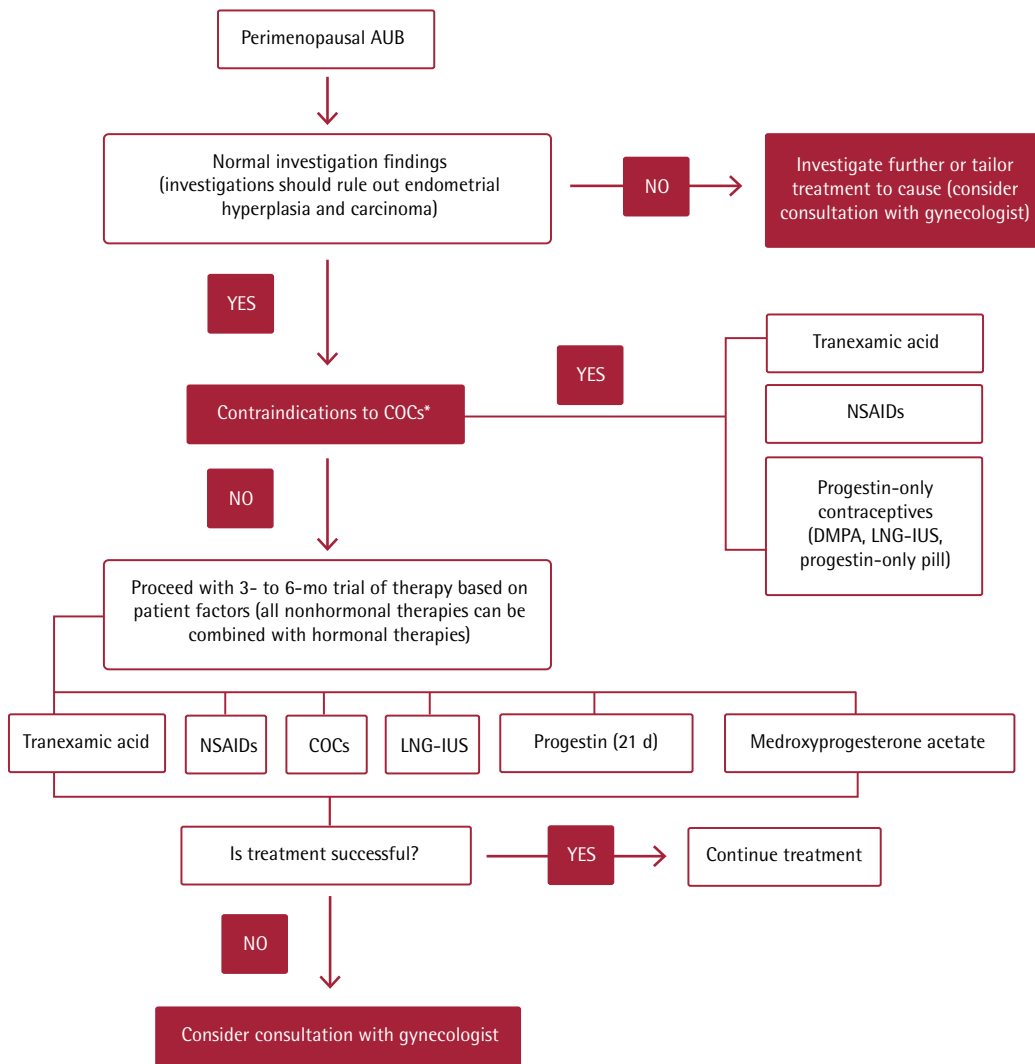
### Treatment options

Candace is in the perimenopausal category of AUB. Because her investigation findings are normal, pharmacologic treatment should be considered first line<sup>5</sup> (Figure 1), and options include hormonal therapy,

nonsteroidal anti-inflammatory drugs (NSAIDs), and antifibrinolytics (Table 1).<sup>6</sup>

**Hormonal therapy.** Hormonal options available for the treatment of AUB include the levonorgestrel intrauterine system (LNG-IUS), combined oral contraceptives (COCs), depot medroxyprogesterone acetate (DMPA), and progestin-only pills.<sup>6</sup> Hormonal options are generally the treatment of choice for AUB, as they assist in regulating the menstrual cycle and decrease the likelihood of unscheduled, prolonged, or heavy bleeding episodes.<sup>7</sup> More women experience adverse hormonal effects with COCs than with the LNG-IUS owing to increased systemic

Figure 1. Treatment algorithm for perimenopausal AUB



AUB—abnormal uterine bleeding, COC—combined oral contraceptive, DMPA—depot medroxyprogesterone acetate, HTN—hypertension, LNG-IUS—levonorgestrel intrauterine system, NSAID—nonsteroidal anti-inflammatory drug, VTE—venous thromboembolism.  
 \*Contraindications to COCs include history of stroke or VTE, uncontrolled HTN, active liver disease, or history of breast cancer.  
 Adapted from Towriss.<sup>6</sup>

**Table 1. Drug therapy options for AUB**

TREATMENT OPTION	FEATURES
Hormonal options	<ul style="list-style-type: none"> <li>• Can be used for prevention and treatment of AUB</li> <li>• Decreases the likelihood of unscheduled or prolonged and heavy bleeding episodes</li> <li>• Good option for women who desire reliable contraception</li> </ul>
• LNG-IUS	<ul style="list-style-type: none"> <li>• Decreases menstrual blood loss by 86% at 3 mo and 97% at 12 mo; 20%-80% of patients are amenorrheic at 1 y</li> <li>• Only has to be inserted every 5 y</li> <li>• Most effective option in obese and overweight women</li> <li>• Avoid in patients with breast cancer or those with recurrent or recent PID</li> <li>• Use with caution in immunocompromised patients or those at high risk of STI</li> </ul>
• COCs	<ul style="list-style-type: none"> <li>• Decreases menstrual blood loss by 40%-50%</li> <li>• Select a COC with <math>\geq 30 \mu\text{g}</math> of ethinyl estradiol</li> <li>• Dosing is continuous or cyclic</li> <li>• Avoid in patients with history of stroke or VTE, uncontrolled HTN, migraine with neurologic symptoms, breast cancer, or active liver disease</li> </ul>
• DMPA	<ul style="list-style-type: none"> <li>• 60%-70% of patients become amenorrheic after first y</li> <li>• Doses administered every 12 wk</li> <li>• Avoid in patients with breast cancer, active liver disease, or liver tumours</li> </ul>
• Progestin-only pills	<ul style="list-style-type: none"> <li>• 50% of women achieve cyclic regularity</li> <li>• 10 mg/d of medroxyprogesterone from cycle d 5-26 (21 d) or 100 mg/d of micronized progesterone from d 14-28 (luteal phase)</li> <li>• Avoid in patients with breast cancer or liver disease</li> </ul>
NSAIDs	<ul style="list-style-type: none"> <li>• Decreases prostaglandin production to promote uterine vasoconstriction and decrease bleeding</li> </ul>
• Naproxen	<ul style="list-style-type: none"> <li>• Can be taken safely with oral contraceptives for dysmenorrhea treatment</li> </ul>
• Ibuprofen	<ul style="list-style-type: none"> <li>• Recommend starting the day before menses and continuing for 3-5 d or until bleeding stops</li> </ul>
• Mefenamic acid	<ul style="list-style-type: none"> <li>• No evidence that one NSAID is better than another; cost varies</li> <li>• Avoid in patients with platelet or coagulation disorders, peptic ulcer disease, and pre-existing gastritis</li> </ul>
Antifibrinolytics	<ul style="list-style-type: none"> <li>• Provides symptomatic treatment only</li> </ul>
• Tranexamic acid	<ul style="list-style-type: none"> <li>• Does not address underlying cause</li> <li>• Avoid in patients with past history of VTE</li> </ul>
Other agents	<ul style="list-style-type: none"> <li>• Usually to be used in consultation with a gynecologist or other specialist</li> </ul>
• Danazol	<ul style="list-style-type: none"> <li>• Used as second-line agents</li> </ul>
• Gonadotropin-releasing hormone agonists	
• Ulipristal	

AUB—abnormal uterine bleeding, COC—combined oral contraceptive, DMPA—depot medroxyprogesterone acetate, HTN—hypertension, LNG-IUS—levonorgestrel intrauterine system, NSAID—nonsteroidal anti-inflammatory drug, PID—pelvic inflammatory disease, STI—sexually transmitted infection, VTE—venous thromboembolism.

Data from Towriss.<sup>5</sup>

absorption of the medication.<sup>8</sup> These complaints include nausea, headache, breakthrough bleeding, fluid retention, breast tenderness, and mood changes.<sup>7</sup>

Ideally, patients should use hormonal options for a trial period of 3 to 6 months to determine their effectiveness.<sup>4</sup>

**Levonorgestrel intrauterine system:** The LNG-IUS is designed to release 20  $\mu\text{g}/\text{d}$  of levonorgestrel for up to 5 years.<sup>9</sup> It has been shown to decrease menstrual blood loss by 86% at 3 months and 97% at 12 months, with 20% to 80% of patients becoming amenorrheic by 1 year.<sup>8,9</sup> Dysmenorrhea and pelvic pain might also improve. Evidence suggests that the LNG-IUS is the most reliable option in obese and overweight women.<sup>10</sup> Some of the most common complaints women have with the

LNG-IUS include irregular bleeding or spotting (especially in the first 3 to 6 months), cramping, and expulsion of the device. A Cochrane meta-analysis review comparing medical treatments with surgical treatments (endometrial destruction and hysterectomy) revealed that the LNG-IUS was less effective for reducing bleeding but provided an equivalent improvement in quality of life.<sup>11</sup> A low-dose LNG-IUS (6  $\mu\text{g}/\text{d}$  for 3 years) is now available in Canada; however, it is not officially indicated for treatment of AUB.<sup>12</sup>

**Combined oral contraceptives:** Combined oral contraceptives are another available hormonal option. There is no evidence to suggest that one type of COC is more effective than another,<sup>6</sup> but selecting a product

with at least 30 µg of ethinyl estradiol is recommended. Combined oral contraceptives decrease menstrual blood loss by 40% to 50% and improve dysmenorrhea.<sup>13</sup> There are many prescribing regimens described in the literature, with the most aggressive being 1 tablet 3 times daily until bleeding ceases, followed by tapering to once daily continuously for 3 months before providing a pill-free interval. However, starting with once-daily dosing with or without the pill-free interval is also appropriate.<sup>5</sup> The use of monophasic COCs in a continuous dosing regimen for up to 3 to 6 months has been demonstrated to be effective in the treatment of AUB; however, there is limited evidence to support the use of continuous triphasic COCs.<sup>14</sup> Transdermal patches or a vaginal ring, used continuously or in a cyclic fashion, are also appropriate options for AUB treatment; however, limited evidence is available for this indication. When prescribing, it is important to review all of a patient's potential risks of thromboembolism (Table 1).<sup>6</sup>

Our patient Candace does not have any contraindications to COCs, but she should be educated about signs and symptoms of venous thromboembolism if this is her treatment of choice.

**Depot medroxyprogesterone acetate:** Intramuscular administration of a 150-mg dose of DMPA every 12 weeks is a suitable option for the management of AUB. Although there are no trials assessing the effectiveness and safety of DMPA in AUB, it has been shown to decrease menstrual blood loss by 60% to 70%, with most women becoming amenorrheic at 1 year<sup>15</sup> when using it for contraception. It can also cause irregular breakthrough bleeding, breast tenderness, nausea, mood symptoms, and weight gain. Additionally, DMPA has been shown to cause a small decrease in bone mineral density, about 1.5%,<sup>16</sup> which is reversible upon discontinuation. Depot medroxyprogesterone acetate could be considered for Candace at 49 years of age, but if she chooses this option she should be educated about appropriate diet and exercise to assist with bone health.

**Progestin-only pills:** Progestin-only pills are another hormonal option available for the treatment of AUB. A 10-mg daily dose of medroxyprogesterone acetate from cycle days 5 to 26 (21 days) or a 100-mg daily dose of micronized progesterone from days 14 to 28 (luteal phase) achieved menstrual regularity in only 50% of women.<sup>15</sup> Luteal phase progestin alone is usually not effective for heavy menstrual bleeding. The long-cycle dosing (21 days) has been shown to decrease heavy menstrual bleeding, but hormonal adverse effects limit its practicality. Complicated prescribing regimens such as cyclic dosing can often lead to nonadherence. Low-dose norethindrone (ie, 0.35 mg/d) has not been studied for the management of AUB.

**Nonsteroidal anti-inflammatory drugs and antifibrinolytics.** All of the hormonal options can be combined with

nonhormonal options such as NSAIDs or antifibrinolytics in order to optimally manage AUB.<sup>13</sup> Antifibrinolytics provide symptomatic relief only, and NSAIDs are less effective than hormonal options.<sup>6</sup> Nonsteroidal anti-inflammatory drugs can increase bleeding in general; however, they cause a paradoxical reaction when treating AUB. Nonsteroidal anti-inflammatory drugs decrease total prostaglandin production to promote uterine vasoconstriction and actually decrease bleeding in AUB.<sup>6</sup> In most cases the benefit of using NSAIDs for AUB actually outweighs the risks. As there are no substantial differences in the effectiveness of different NSAIDs,<sup>17</sup> choice might be based on cost and tolerability.

**Surgical treatment.** Surgical treatment is not considered first line in Candace's case owing to its invasive nature. Additionally, she has not failed medical therapy yet, has no contraindications to drug treatment, and she is not anemic.<sup>5</sup> It is worth noting that approximately 50% of women who receive drug therapy eventually choose surgical therapy owing to refractory bleeding or a desire for definitive treatment.<sup>18,19</sup>

*You share with Candace that younger patients with AUB often prefer COCs and NSAIDs but that perimenopausal women usually prefer the LNG-IUS.<sup>20-22</sup> You also explain to her that the LNG-IUS is the most reliable hormonal choice considering her increased body mass index.*

*Candace feels cautious about the LNG-IUS (despite the fact the endometrial biopsy was well tolerated) and decides to try a COC. You prescribe a 30-µg ethinyl estradiol formulation and plan for a follow-up visit to review this treatment in 3 months' time. You also prescribe 1000 mg of naproxen to take the day before menses, then 500 mg twice daily for 3 to 5 days to both help with symptoms and decrease bleeding.*

*However, 2 months later Candace returns telling you that her periods are lighter but lasting 9 days, which she finds unacceptable. She would like to revisit other treatment options.*

Candace might achieve better control of her flow if she continues the initial COC for a few more months. Changing the COC formulation to one with a higher estrogen component or to another type of progestogen might be helpful.<sup>20</sup> There is no evidence as to which works best.<sup>6</sup>

*Candace tells you that a friend at work has had good success with the LNG-IUS and she would like to try this. You mention that the up-front cost is approximately \$350, but that overall it is a cost-effective option at \$70 a year. You insert the device without complication. You follow up with Candace in the clinic 3 months later. She is very pleased with the LNG-IUS. After having some*

intermittent spotting and cramping over the first month, things have settled and she now has only a few days of spotting, which likely corresponds with her menses. 🌸

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#### Competing interests

RxFiles and contributing authors do not have any commercial competing interests. RxFiles Academic Detailing Program is funded through a grant from Saskatchewan Health to Saskatoon Health Region; additional "not for profit; not for loss" revenue is obtained from sales of books and online subscriptions. No financial assistance was obtained for this publication.

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