Abnormal Uterine Bleeding During the Reproductive Years—Terminology and Treatment

a report by

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Many confusing terms are used to describe several very common menstrual symptoms of the reproductive years. Healthcare professionals who treat abnormal menstrual cycle regularity, frequency, duration, and/or amount of bleeding have heard and used inexact terms such as menorrhagia, amenorrhea, and dysfunctional uterine bleeding (DUB) to describe abnormal patterns of menstrual bleeding. A recently published consensus statement strongly recommended that these inexact terms be abandoned and replaced with a more simple and descriptive taxonomy so that communication and research protocols are clarified and standardized. The most important step in the management of the symptom of abnormal uterine bleeding (AUB) is diagnosis. In most cases, history and physical exam, blood count, ultrasound, and/or biopsy will provide the necessary information. Once the initial work-up is completed, and assuming these results do not identify significant pathology that warrants more immediate invasive intervention, treatment usually begins with medical therapy, increasing to invasive treatment only after medical management fails. Medical treatment can consist of non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives (OCs), oral progesterone, a progesterone-releasing intrauterine device (IUD), or antifibrinolytics. If these first-line treatments fail, more invasive surgical options should be considered.

Abnormal uterine bleeding (AUB) is a very common menstrual symptom during the reproductive years. Many terms have been used to describe the abnormal patterns of menstrual bleeding, including its absence (amenorrhea), its lack of regularity or duration of flow (menorrhagia or metorrhagia), or both (menometorrhagia). Sometimes the amount of flow is abnormal (hyper- or hypomenorrhea). Patients are not familiar with these terms and healthcare professionals often use them to mean different things, adding to the confusion. Recently, a group of international experts convened to discuss the different uses and meanings of these and other terms to describe AUB.[1] The consensus was that the symptom of AUB should be simply described in terms of its patterns as irregular or absent, frequent or infrequent, prolonged or shortened, and heavy or light. *Table 1* lists frequently used terms that are confusing. In this article, we will use AUB to describe abnormally heavy or abnormally timed (frequent or infrequent) uterine bleeding experienced by a non-pregnant woman during her reproductive years. We will use simple descriptive language to indicate the amount and timing of this common symptom during the reproductive years.

Case History

SW is a 37-year-old, gravida four, para three, abortus one woman complaining of six months of "periods that have gone crazy." She complains that she missed six days of work last month because of heavy bleeding. Her absence from work increased from the two to three days a month that she missed in each of the previous four or five months. While the heavy days seemed to be predictable before—occurring every 32 days—now she is having more trouble knowing when they will come, so she takes an entire box of super-thickness heavy-duty pads to the office every day.

She has no other medical problems, is not overweight, and takes no medications. She had her first menstrual period at 12 years of age and, other than several brief times when she was under excessive stress, her menses have always been regular and predictable. She is sexually active with her husband, who uses condoms. She has no symptoms of systemic disease. Her last gynecological exam was 10 months ago. At that time, her Papanicolaou (Pap) smear test was normal. She has never had a mammogram. SW's physical exam is unremarkable, except for dark red blood in her vaginal vault.

In most cases of AUB, the problem is subjectively defined. Patients will say, "I am bleeding too much" or "I bleed too frequently." There is usually no anemia or other pathology to be treated. Thus, successful treatment is defined as improving the patient's quality of life by relieving her complaint

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Table 1: Frequently Used Terms to Describe Abnormal Uterine Bleeding*

Amenorrhea	Absence of menses (usually for 6 months or more)
Menorrhagia	Heavy menstrual bleeding at regular intervals
Metorrhagia	Irregularly timed menstrual bleeding
Menometorrhagia	Heavy, irregularly timed menstrual bleeding
Hypermenorrhea	Heavy menstrual bleeding
Hypomenorrhea	Light menstrual bleeding

**These terms are not intrinsically descriptive, may mean different things when used by different healthcare professionals, and are confusing and difficult to control as part of research protocols for the study of abnormal uterine bleeding (AUB).*

Table 2: Independent Risk Factors for Endometrial Hyperplasia and Carcinoma in Women with Abnormal Uterine Bleeding

Factor	Prevalance (%)	Odds Ratio (95% CI)	p-value
All patients	4.9	–	–
Weight ≥90kg	12.7	5.5 (2.9–10.6)	<0.0001
Age ≥45 years	7.9	3.1 (1.5–6.1)	0.0016
Weight ≥90kg and age ≥45 years	22.2	–	–
Weight ≥90kg and age <45 years	2.3	–	–
Family history of colon cancer	–	5.0 (1.3–19.1)	0.0182
Infertility	–	3.6 (1.3–9.9)	0.0127
Nulliparity	–	2.8 (1.1–7.2)	0.0267
Family history of endometrial cancer	–	5.8 (1.1–28.6)	0.0392

CI = confidence interval. Source: Vilos G, Lefebre G, Graves G, Guidelines for the management of abnormal uterine bleeding, SOGC Clinical Practice Guidelines No.106, J Obstet Gynaecol Can, *2001.*

of excessive vaginal bleeding and allowing her to resume normal daily activities. The usual first step is to collect a gynecological history and perform a physical examination. A key distinction to make on history is whether cycles are likely to be ovulatory or anovulatory. Ovulatory AUB usually presents with heavy but predictable cyclic flow and no intermenstrual bleeding. Attention should be paid on examination to confirm that bleeding is from the uterus and not vaginal in origin. Missing a vaginal lesion and treating for uterine bleeding can delay more appropriate therapy.

Attempting to accurately estimate the amount of blood loss at the time of history taking is generally not recommended. Tools such as the pictorial blood loss assessment chart (PBAC) are accurate but not particularly useful in clinical practice. This is because the problem of excessive bleeding is best defined in terms of a woman's experience, not objective measurements. Therefore, not being able to accurately estimate blood loss does not hinder diagnosis or treatment.[2]

SW's Pap smear test was repeated at a time when bleeding was minimal and normal. The hemoglobin level was 12.1gm/dl, the hematocrit level was 36.1%, and the white blood cell (WBC) count was 5,600 cells/mcl; all values were within normal limits for a 37-year-old non-pregnant woman. Urine human chorionic gonadotropin (hCG) was negative.

Laboratory examination should include a Pap smear test (if not recently performed) and blood cell counts. In a patient with regularly timed heavy menses, anemia, and an otherwise unremarkable history and physical examination, it may be appropriate to treat with iron and/or oral contraceptives (OCs) without further evaluation. If cycles are irregular, indicating chronic anovulation, cyclic progestins may reduce bleeding but they are usually of no value in ovulatory cycles because they do not reliably prevent ovulation and adequate endogenous progesterone is already present.

Uterine structural abnormalities may be identified using a variety of imaging techniques including magnetic resonance imaging (MRI), office hysteroscopy, transvaginal ultrasound (TVU), and saline infusion sonohysterography (SIS). The primary goal of these evaluations is to rule out uterine fibroids, particularly submucosal ones that intrude into the uterine cavity, and/or polyps. The relatively low cost, wide availability, and adequate sensitivity of TVU make it a good initial choice, and it may be performed as part of the initial evaluation or delayed if physical examination is normal. MRI may be most accurate and is subject to less interobserver variability than the other techniques, but may be more costly and less readily available.[3] Accurate imaging is particularly important in a woman with an enlarged or irregular uterus, or in whom initial first-line treatment has failed.

Other investigations are usually dictated by findings on history and physical examinations, and include a mid-luteal progesterone to confirm ovulation when cycles are still reasonably regular, a thyroid-stimulating hormone (TSH) level if there are symptoms present that are suggestive of thyroid dysfunction, follicle-stimulating hormone (FSH) if menopausal status is in doubt, leutinizing hormone (LH) (in conjunction with FSH) if polycystic ovary syndrome (PCOS) is suspected, and tests for coagulation abnormalities (e.g. von Willebrand's disease) in patients with a history of heavy bleeding since menarche or with other historical risk factors. To avoid false-positive findings and unnecessary cost, these studies should not be performed routinely, but rather should be applied thoughtfully and using clinical judgment.

SW's transvaginal ultrasound showed several 1–2cm uterine fibroids completely within the uterine wall (intramural). The endometrium was 12mm thick and there was no evidence of polyps.

Endometrial thickness in a pre-menopausal patient is not helpful in ruling out cancer. Many authors have suggested rules for when biopsies should be performed, but all such rules tend to either subject too many women to unneeded biopsies or potentially miss cancers, so clinical judgment is key (see *Table 2*). Certainly, women over 40 years of age who have anovulatory AUB should undergo endometrial sampling. However, even women as young as 18 years of age who have had several years of anovulatory cycles (particularly if they are obese) may have endometrial cancer, highlighting the difficulty of creating clear 'rules' for management.[4] Office endometrial biopsy can be accomplished safely and comfortably in most women, even those who have not delivered a baby. Dilation and curettage should not be a first-line diagnostic tool and, except in the setting of acute hemorrhage, has no role in the treatment of AUB.[2,5]

Non-invasive Treatment

With a history that is suggestive of AUB and no abnormal findings on history or physical exam (e.g. suggestive of coagulopathy or the presence of submucous fibroids), several non-invasive treatments may be appropriate (see *Table 3*). One primary consideration in treatment is whether the patient desires contraception. For a woman who wants long-term contraception, a levonorgestrel-releasing intrauterine system

(LNG-IUS) (Mirena [MB1]) is an excellent treatment. The LNG-IUS has proven efficacy (as much as 95% reduction in blood loss) and safety, and provides nearly failure-free contraception. The long-term efficacy and safety (even in nulligravid women) of these devices is well proven.[2,6] A randomized controlled trial, the Effectiveness and Cost-effectiveness of Levonorgestrel-containing Intrauterine System in Primary Care Against Standard Treatment for Menorrhagia (ECLIPSE), is currently under-way to compare treatment with this device with pharmacological treatment.[7]

For women who require contraception but do not want IUDs, combined OCs are another option. Despite the frequent use of OCs for the treatment of AUB, there are remarkably few data on their effectiveness.

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One study of a 30mcg ethinyl estradiol pill and another of a 35mcg pill showed moderate reductions in abnormal bleeding of about 40–50%. There are no data to support the use of lower-dose OCs to treat AUB.[2,8,9]

For patients who do not require contraception, oral progestins such as norethindrone (Aygestin and others) given at 15mg for 21 days (usually days five to 26 of the cycle) reduce blood loss by more than 80% (a substantial reduction, but less than the reductions seen with the LNG-IUS). Typically, treatment regimens of 11–14 days of progestins are less effective than the 21-day regimen but have fewer side effects.[10]

NSAIDs are another good non-contraceptive choice for the medical management of anovulatory AUB, as is tranexamic acid (Cyklokapron), although the oral form is no longer available in the US.[6,10–12] NSAIDs are inexpensive, easily accessible over the counter and on prescription, and effective for bleeding and dysmenorrhea. As they are used when needed—starting with the day of bleeding, or, if predictable, the day before, and continuing until bleeding ceases—some of the problems associated with long-term use (e.g. gastric pain and bleeding) are reduced. They are less effective than the LNG-IUS and the 21-day progestin regimen (reducing blood loss by only about 50%). Women with fibroids were excluded from the NSAID trials, so little is known about their effectiveness in that group.[11]

Injectable progestins (medroxyprogesterone acetate [Depo-Provera]) and implantable progestins (etonogesrel [Implanon]) eliminate menses in many women who use them for contraception. Those products are likely to reduce bleeding in women with AUB, but the effect may take up to six months to be noticeable. Gonadotrophin-releasing hormone analogs (GnRHa [Lupron]) reduce menstrual bleeding but have significant side effects such as bone loss, hot flashes, and vaginal dryness, not all of which can be controlled with 'add-back' estrogen, so are not an ideal first-line treatment for AUB.[13]

Table 3: Comparative Table of Medical Therapy for the Treatment of Heavy Menstrual Bleeding

Drug	Mean Reduction in Blood Loss (%)	Women Benefiting—Proportion with MBL <80ml/cycle (%)
Levonorgestrel IUS	94	100
Oral progesterone (days 5–25)*	87	86
Tranexamic acid**	47	56
NSAIDs	29	51
OC pill	43	50
Danazol	50	76
Oral progesterone (luteal phase)	-4	18

** Based on only one randomized controlled trial. **Not currently available in the US. IUS = intrauterine system; NSAIDs = non-steroidal anti-inflammatory drugs; OC = oral contraceptive; MBL = menstrual blood loss.*
Source: Guidelines for the Management of Heavy Menstrual Bleeding. Working Party on behalf of the National Health Committee. New Zealand 1998. Available at: www.nzgg.org.nz/guidelines/0032/HMB_fulltext.pdf

Table 4: Contraindications for Second-generation Endometrial Ablation Techniques (Reported by Manufacturer)

Contraindictaion	Microwave	Cavaterm	Thermachoice
Uterine cavity size (cm)	>14	>10	>12
Previous surgery or trauma leading to uterine wall thickness of at least 8mm	✓	–	–
Previous classic Cesarean section as scar would be positioned in the operative field	✓	–	–
Previous ablation/resection as this thins the uterine wall	✓	–	–
Fibroids distorting the uterine cavity	✓	–	–
Repeat ablations should never be performed in conjunction with mechanical preparation	✓	–	–
D&C should not be performed as preparation	✓	–	–
Women who are pregnant or who wish to become so should not undergo EA	✓	✓	✓
Active pelvic inflammatory infection	✓	✓	–
Undiagnosed vaginal bleeding	✓	✓	–
Known or suspected endometrial carcinoma	✓	✓	✓
Gross abnormalities such as myomas that prevent the ball lying uniformly on the endometrium	–	✓	✓
Separate uterus (septum dividing the uterus in two) or other abnormalities/lesions that would result in inadequate balloon contact	–	✓	✓
Uterine wall weakness	–	✓	–
Cervical canal <6cm in length	–	✓	–

D&C = dilation and cutterage; EA = endometrial ablation.
The wording used in this table has been taken from information provided by the manufacturer of each device. Where a dash is present, this indicates that the contraindication was not expicitly stated by the manufacturer.
Source: Garside, 2004.[16]

Invasive Treatment

In general, non-invasive treatment should be offered as first-line therapy. However, the long-term recurrence rate of AUB treated with oral medications is high, so many women who begin with oral therapy will need to move on to invasive therapy eventually. The LNG-IUS appears to be an exception, providing high levels of long-term relief with low recurrence risks.[14]

There are several important considerations with invasive treatment of AUB: will a reduction in menstrual bleeding be a successful outcome from the patient's point of view, or is complete absence of bleeding desired? How important is a rapid return to normal daily activity? Does the women want to retain her fertility? Does the woman want to retain her uterus? Bear in

mind that a woman may want to retain her uterus even when she is no longer considering child-bearing.

If the woman does not want to retain her uterus and wants complete absence of uterine bleeding, hysterectomy may be a reasonable choice. In these circumstances, the higher complication rate from hysterectomy is outweighed by its higher success rate at achieving absence of bleeing

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(100% success rate compared with 10–40% for the various endometrial destruction techniques).[2,15] If conserving fertility is an issue, LNG-IUS is the best option unless a polyp or other intracavitary lesion appears to be the cause of bleeding. For polyps and most fully intracavitary myomas, hysteroscopically directed removal is appropriate.

SW wants no more children and does not desire to retain her uterus. A four-month trial of OCs with NSAIDs did not give her adequate relief. She simply wants to get back to a state where bleeding does not interfere with her work or social life. In a patient like SW with fibroids ≤3cm in diameter that are not intracavitary, endometrial destruction/ablation is an excellent option. The so-called 'first-generation' techniques, including rollerball ablation (REA) and transcervical resection (TCRE), require hysteroscopic visualization of the endometrium. These methods have been in use since the early 1990s and at least five randomized clinical trials have compared ablation with hysterectomy, with largely favorable results.[2] Hysterectomy results in slightly higher satisfaction and quality of life than endometrial ablation, but at the cost of substantially longer hospitalization time and more complications. Unless complete absence of bleeding is a primary goal, or the risk for requiring repeat surgery is extremely concerning, ablation should be offered over hysterectomy.[16]

In recent years, first-generation destructive techniques have been largely superceded by 'second-generation' techniques that do not require direct visualization of the endometrium. Unless direct visualization is required (e.g. to treat a polyp or myoma), second-generation techniques are a better choice, requiring less time and reducing risk.[17] Second-generation techniques include thermal balloon endometrial ablation (TBEA), microwave endometrial ablation (MEA), hydrothermal ablation (HTA), endometrial cyroablation (ECA), and radiofrequency ablation (RFA). These systems have been compared in various combinations without demonstrating a consistent advantage of one system over another. Each manufacturer reports different contraindications, but the evidence suggests that with proper training in their use, any of these methods will produce good results[2] (see *Table 4*). With most ablation methods (except TBEA), 'chemical' endometrial thinning with a GnRHa before the procedure improves outcomes and speeds the procedure; however, even without GnRHa use, satisfaction and safety are high.[18] With all endometrial destructive techniques, women must be advised to use adequate contraception afterwards. In MEA, scheduling of surgery during the post-menstrual phase is an alternative to GnRHa-induced endometrial thinning. SW was offered hysterectomy or TBEA (the procedure with which the physician was most comfortable). She elected to undergo TBEA and underwent the procedure without GnRHa preparation during the post-menstrual phase of her cycle. Her symptoms improved by the next cycle and she remains quite satisfied with the results. She and her husband continue to use condoms for contraception.

Treating AUB has become much easier over the last decade. Women and their healthcare professionals can improve their communication with each other by using simple descriptive terms for AUB, and they have more effective invasive and non-invasive treatments to choose from. The primary goals when evaluating and treating AUB are to rule out significant pathology (such as cancer) and then, in most cases, to improve patient quality of life by restoring normal daily activites. Accurate diagnosis is important because anovulatory bleeding, ovulatory bleeding, and bleeding related to fibroids may all be treated differently. Many key treatment decisions depend on patient preferences: for example, the decision to use a LNG-IUS or OCs, or the decision to have a hysterectomy or ablation therapy. Luckily, when appropriately selected, many different choices produce good results: reduction in bleeding, improved quality of life, and high satisfaction. ■

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