Chapter 12
Premenopausal Women

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Anemia in a menstruating woman may be falsely attributed to heavy periods, and an opportunity to recognize an occult gastrointestinal bleed could be missed.

A woman of reproductive age who reports abnormal menstrual bleeding deserves further evaluation. Her concerns may include a change in her typical bleeding pattern or an increase in blood loss. Her evaluation begins with a careful history, and her provider should have a basic understanding of what constitutes normal bleeding and when further testing or referral is warranted.

Normal Menses

A normal menstrual cycle requires complex coordination between multiple systems: neural, endocrine, hematologic, and other pathways interact to maintain this fundamental part of the reproductive system. Any insult to this process, including stress, weight change, illness, or medications, may upset this balance and change an individual's typical pattern.

Normal menstrual flow usually lasts about 5 days, and the normal cycle duration (including bleeding days) is 21–35 days.

Some women never establish normal menses and may report abnormal bleeding since menarche. These women may have an underlying bleeding disorder, such as von Willebrand disease (VWD), and a longstanding history of heavy menses. Those patients will likely report other symptoms, such as frequent nosebleeds, that can help steer a provider toward the correct diagnosis.

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Some women may not realize that their menses are abnormal, especially if they have always been heavy, so it is important to quantify the amount of blood lost in a standardized fashion. Conversely, some women may report heavy bleeding, when in fact, the amount of blood lost is within the normal range.

Bleeding Interval

Typical menstrual cycles occur at a regular frequency anywhere from 24 to 38 days in duration. Bleeding usually occurs for 4.5–8 days. More than 9 days may be considered abnormal [1].

Certain types of contraceptives may cause irregular bleeding outside of normal menstruation. This is especially true in the first 1–3 months of use. Thirty percent of women using a combined estrogen-progestin pill, a patch, or the ring may see unscheduled bleeding during the first month; 25% with progestin only contraceptives during the first year; and with the copper-IUD [2].

Anovulatory bleeding is defined as uterine bleeding that does not result in response to ovulation.

In adolescents up to 18 years old, anovulatory bleeding may occur due to an immature or dysregulated hypothalamic-pituitary-ovarian axis. This is not considered pathologic in nature.

In patients aged 40+ until menopause, anovulatory may be due to a physiologic decline in ovarian function. However, a range of pathologies may also cause anovulatory bleeding, and therefore should not be ruled out in favor of physiologic decline [3].

Quantifying Bleeding

During menses, the average amount of blood lost is 34 ml ± 2.4 ml per month. The amount is generally consistent in an individual patient from onset of menarche to menopause, so significant changes in the amount lost may indicate other factors at play [4].

Heavy menstrual bleeding (HMB) lasts longer than 7 days or exceeds 80 ml per period. Women with HMB may develop iron deficiency anemia, which can be profound. On average, 1.0 mg of iron is lost per 60 ml of blood during menses. The critical loss at which iron deficiency may occur is around 1.2–1.6 mg of iron, which is about 72–96 ml of blood. It must be noted however, that the exact amount needed to cause an anemic state depends on dietary intake and absorption as well as overall state of health of the patient [4].

Our ability to quantify menstrual blood loss is limited in the clinical setting. While the average woman doesn't know the volume of blood lost with menses, she

can usually report the number of sanitary products she uses on a typical day of bleeding. The provider may ask what products she is using (see below), how often she changes them, and whether they are saturated when they are changed. The provider should also ask whether the patient passes blood clots or bleeds through clothing or bedding [5].

There are many different sanitary products available to women, including pads, tampons, menstrual cups, and absorbent underwear. Some products have different levels of absorbency or come in different sizes to accommodate different volumes of flow. The approximate volumes held by different products are outlined in Table 12.1.

The most commonly used sanitary products are tampons and pads. Sanitary pads vary widely in their absorbency, which can make it difficult to quantify blood loss. If a woman changes the type or brand of pad she is using, she may report needing to change it more or less frequently, when in fact, her bleeding is unchanged [6].

Patients must not just be asked how many times per day that they change their product, they must also be asked why. Some women may change them on a schedule whereas others may only change them when they're fully saturated [6]. A sample set of questions is included in Table 12.2.

Table 12.1 The maximum volumes held by various sanitary products based on data from the FDA and various product listings by brands

Sanitary product	Volume (ml)
Pads	
Liner	–
Regular	–
Maxi pad	–
Tampons	
Light	<5.5
Regular	5.5–8.5
Super	8.5–11.5
Menstrual cups	
Slim/small	17–22
Regular	30
Large	32
Underwear	10–15

Table 12.2 Suggested questions to characterize uterine bleeding [6]

When was the first day of your last menstrual period and several previous menstrual periods?
Is there a possibility that you could be pregnant?
How heavy is your bleeding?
Do you pass blood clots?

Abnormal Uterine Bleeding

Terminology

The classification system for abnormal bleeding was updated in 2011 by the International Federation of Gynecology and Obstetrics (FIGO), and this new nomenclature has been adopted by the American College of Obstetricians and Gynecologists (ACOG) [3].

Although the previous system for classifying abnormal bleeding has been replaced, familiarity with the old terms may be useful when reviewing patient records or older publications, shown in Table 12.3 below.

Additionally, the older phrase *dysfunctional uterine bleeding* (DUB) has been replaced by the term *abnormal uterine bleeding* (AUB), which includes *heavy menstrual bleeding* (HMB) and *intermenstrual bleeding* (IMB). HMB and IMB may occur alone or together in an individual patient. The term DUB should no longer be used, but it may still be seen in patient records [3].

The FIGO classification system was created to improve standardization and specificity when describing AUB in reproductive-aged women. The system does not apply to pregnant women or postmenopausal women. The new classification system incorporates bleeding pattern and etiology, and it is referred to by the acronym PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) [7].

PALM-COEIN

In the PALM-COEIN system (Fig. 12.1), PALM represents structural causes of AUB (polyps, adenomyosis, leiomyoma, malignancy and hyperplasia), and COEIN represents nonstructural causes (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified). Understanding the fundamentals of this classification system can provide some guidance to providers when they begin to evaluate a patient with AUB [7].

Table 12.3 Preferred terminology per ACOG recommendations to characterize bleeding and pain complaints [1]

Polymenorrhea	Cycle lasting less than 21 days
Oligomenorrhea	Cycle lasting longer than 35 days
Menorrhagia	Menstrual blood loss greater than 80 ml
Metrorrhagia	Bleeding between periods
Menometrorrhagia	Heavy menstrual bleeding with intermenstrual bleeding

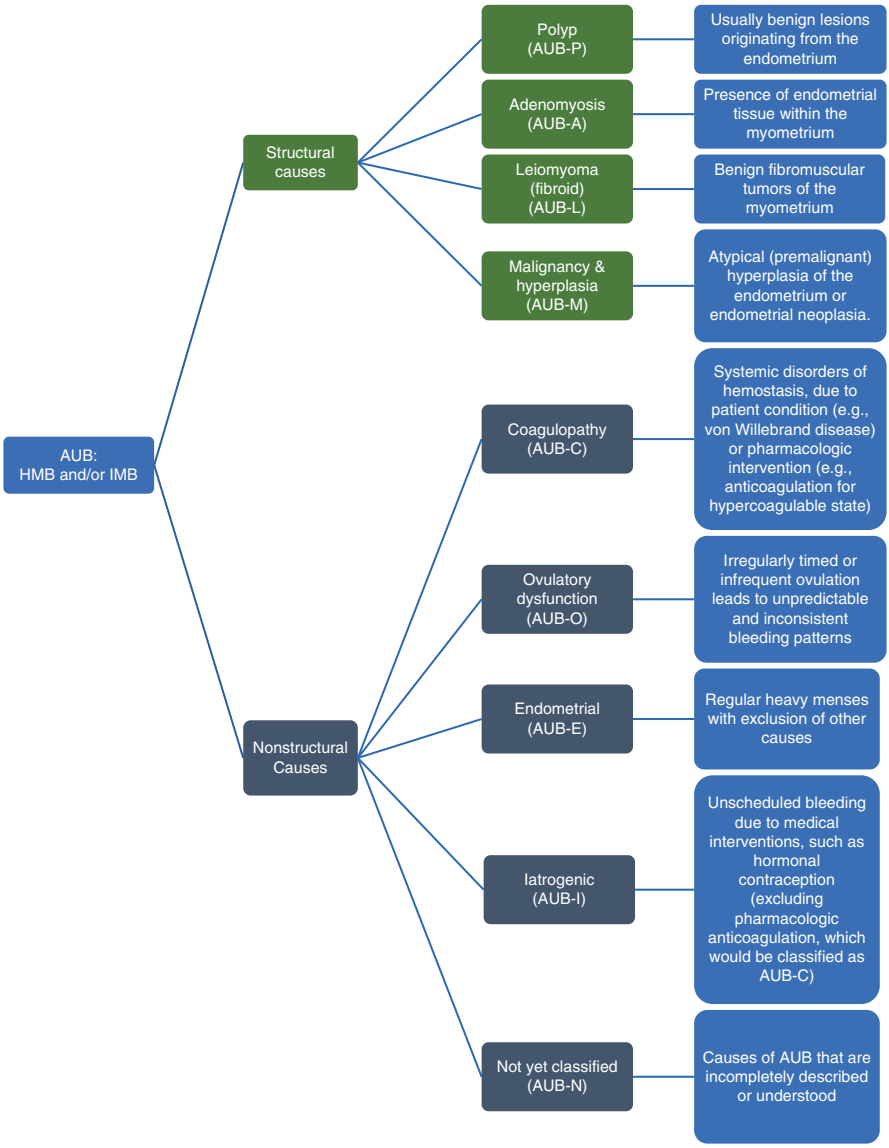

Fig. 12.1 Classification of AUB based on current PALM-COEIN system. [Adapted, 7]

Pregnancy

The possibility of pregnancy should always be considered in sexually active women. Pregnancy and miscarriage can lead to a change in a woman's bleeding pattern, and these diagnoses can be easily excluded with a point-of-care urine test. Failure to promptly diagnose pregnancy may occur in women who report a history of irregular menses or infertility. All contraceptive methods have the potential to fail; even surgical sterilization, so a sexually active woman who reports using contraception can still become pregnant, even if that likelihood is low.

AUB Etiology by Age

The most common causes for AUB vary at different stages of the reproductive lifespan. While anovulation and coagulation defects account for a greater proportion of AUB in adolescents, older reproductive-aged women experience more AUB from pregnancy and sexually transmitted infections [8].

As women age, the incidence of uterine fibroids, polyps, and adenomyosis all increase, and as women approach menopause, ovulation becomes less frequent, so anovulation once again accounts for a significant amount of AUB cases.

The risk of gynecologic malignancy also increases with age, and cancer in any part of the reproductive tract can lead to vaginal bleeding. Globally, cervical cancer is the most common gynecologic malignancy and the leading cause of death from gynecologic cancer. Its incidence is highest in regions without effective screening programs, especially in less developed countries [9].

In more developed countries, uterine cancer (most of which occurs in the endometrium) is the most common gynecologic malignancy. Because endometrial cancer leads to AUB, many of these women present for care early enough that the diagnosis is made at an early stage, when outcomes tend to be better.

Endometrial Hyperplasia and Cancer

Endometrial hyperplasia describes a range of histopathologic changes to the uterine lining. The World Health Organization classified endometrial hyperplasia into two broad categories:

- Hyperplasia without atypia, which contains low levels of mutations and normal glandular structure. These structures may be simple or complex. This type of pathology has only a 1–3% chance of becoming an invasive carcinoma.
- Atypical Hyperplasia/Endometrioid Intraepithelial Neoplasia, whereby there are mutations and structural changes that are typical for invasive carcinoma. These patients are at a very high risk of developing endometrial cancer [10].

There are multiple risk factors for endometrial hyperplasia in women, most notably unopposed estrogen stimulation of the endometrium, which causes increased cell proliferation and growth. Without progesterone to stimulate shedding of the endometrium, the unopposed estrogen can lead to changes in the tissue causing hyperplasia. This can come from exogenous estrogen exposure as with use of estrogen agonists, obesity, early menarche or late menopause, or nullparity.

There are several different forms of endometrial cancer, but 80% are endometrioid adenocarcinoma. This type is graded on a scale of 1–3 based on the level of differentiation of the tissue and it develops from endometrial hyperplasia [11]. As with hyperplasia, endometrial cancer is dependent on estrogen stimulation for growth. Other forms include papillary serous carcinomas, clear cell carcinoma, mixed cell type, and carcinosarcomas [12].

Both hyperplasia and cancer can cause increased or prolonged bleeding during menstruation or off-cycle in premenopausal women. As the disease progresses, patients may present with pressure or pain in the uterus, enlargement of the uterus and increased girth of the abdomen, bloating, or early satiety [8].

Lynch Syndrome

Lynch Syndrome, formerly called Hereditary Nonpolyposis Colorectal Cancer (HNPCC), is an autosomal dominant hereditary mutation in DNA mismatch proteins that leads to a high risk of certain types of cancer, including colorectal, endometrial, ovarian, and breast cancer [13]. Thus, patients with a family history of this disease should be screened and properly counseled [14].

The most common extracolonic manifestation of Lynch syndrome is endometrial cancer, and the mean age at diagnosis (46–54 years) is about 10 years sooner than in the general population. Because this age range overlaps with perimenopause in many women, AUB may be attributed to anovulation, which may delay diagnosis [15].

Women known to be affected by Lynch syndrome should undergo increased surveillance for endometrial cancer via annual endometrial sampling beginning at age 30–35 or 5–10 years prior to the earliest age of first diagnosis of Lynch-associated cancer of any kind in the family [15].

Initial Evaluation of AUB

Figure 12.2 illustrate management steps for AUB. Taking a thorough history can elicit a sound differential in many women with AUB. This can lead to an expedited diagnosis while minimizing superfluous tests, and initial studies should be based on the patient's history and physical exam.

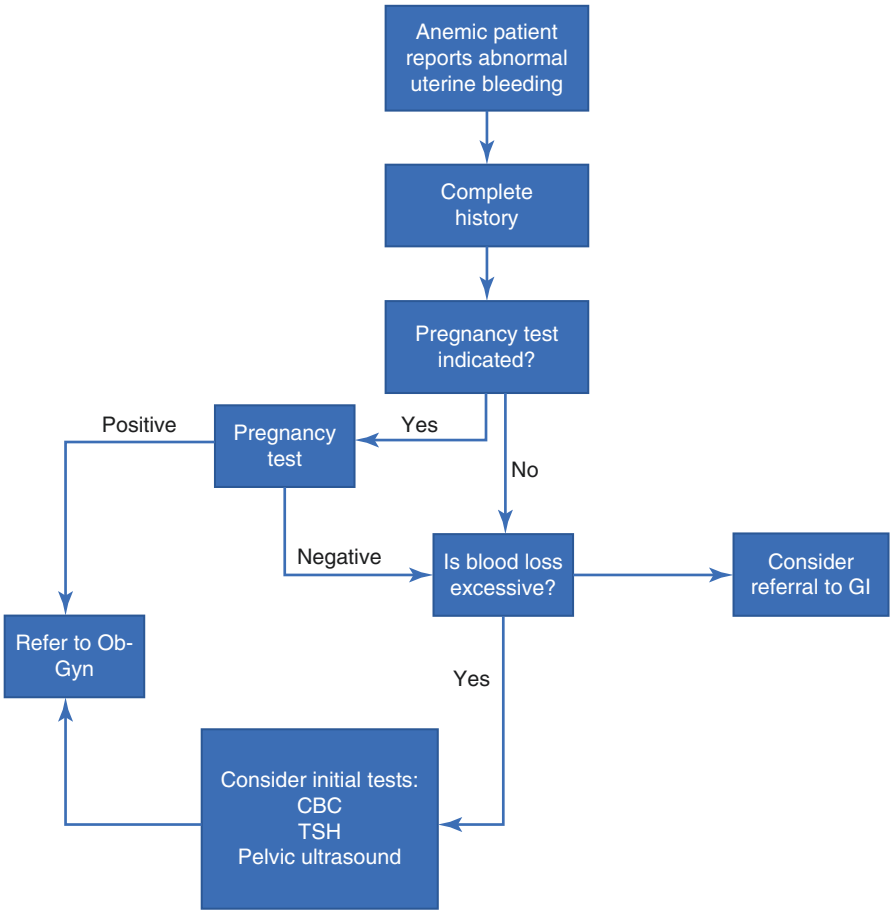

Fig. 12.2 Algorithm for initial work up including labs and imaging studies. [Adapted, 1]

Basic labs to consider:

- Pregnancy test
- Complete blood count (CBC)
- Thyroid-stimulating hormone (TSH)
- Gonorrhea and chlamydia screening
- Pap smear*
- Coagulation studies*
- Prolactin*

* *If indicated by history*

Pelvic ultrasound, including transvaginal evaluation, is the gold standard for imaging the pelvic organs, and it should be considered as part of an initial workup. A CT of the abdomen and pelvis may identify abnormalities in the uterus or ovaries, but ultrasound may still be necessary to better characterize the findings [8].

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