Abnormal Vaginal Bleeding During the Early Reproductive Years

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Abstract

New terminology was introduced by the Menstrual Disorder Working Group of the International Federation of Gynecology and Obstetrics (FIGO) and approved by ACOG several years ago to facilitate accurate descriptions of all dimension of each woman's bleeding. These descriptors better characterize abnormal uterine bleeding patterns than the older imprecise terms, such as "dysfunctional uterine bleeding" and "menorrhagia". The new PALM-COEIN classification system was implemented shortly thereafter to standardize reporting of *etiologies* of abnormal bleeding. Utilizing these new tools and current practice guidelines, this chapter will provide an overview of the differential diagnoses, evaluations, and treatment of women presenting with abnormal uterine bleeding from adolescence through the end of a woman's reproductive years.

Keywords

Abnormal uterine bleeding • Amenorrhea • Infrequent bleeding • Postcoital bleeding • Intermenstrual bleeding • Heavy menstrual bleeding • PCOS

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1 Introduction

Information about uterine bleeding is an essential vital sign for reproductive age women. At every clinical encounter, a woman should be asked about the normalcy and timing of her last menses. At initial and periodic well-woman visits, a full description of a patient's menstrual bleeding should be documented, including the frequency of her bleeding, duration of flow, volume of flow,

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Table 1 Menstrual parameters in the reproductive years

Clinical dimensions of menstruation and menstrual cycle	Descriptive term	Normal limits (5th–95th percentiles)
Frequency of menses, days	Frequent	<24
	Normal	24–38
	Infrequent	38
Regularity of menses: cycle-to-cycle variation over 12 months, days	Absent	No bleeding
	Regular	Variation ± 2–20
	Irregular	Variation >20
Duration of flow, days	Prolonged	>8.0
	Normal	4.5–8.0
	Shortened	<4.5
Volume of monthly blood loss, mL	Heavy	>80
	Normal	5–80
	Light	<5

and cycle-to-cycle variability. Table 1 shows the latest FIGO definition as well as normal values and acceptable words to use to describe abnormal patterns of bleeding. Self-characterization of bleeding, e.g., "irregular" versus "normal," is not sufficient; numerical estimates are needed (Fraser et al. 2011).

Abnormal uterine bleeding patterns range from complete absence of any uterine spotting to excessive and/or prolonged bleeding. Many different reproductive and general health conditions can result in abnormal bleeding, so evaluation should always be comprehensive. When a woman first complains of "abnormal bleeding," careful questioning can provide the information needed to describe her bleeding patterns utilizing the terms in Table 1 (Fraser et al. 2011). A through physical exam is needed because it may reveal the etiology of the abnormal uterine bleeding. At the end of a patient's first visit, the assessment includes the description of her menses using the FIGO terms, the differential diagnoses, and planned diagnostic studies as well medications for the woman to use as bridge therapy until her diagnosis is confirmed.

Once the results of diagnostic tests are available, the PALM-COEIN classification system

Table 2 PALM-COEIN classification of abnormal uterine bleeding

PALM: structural causes	COEIN: functional causes
Polyp (AUB-P)	**C**oagulopathy (AUB-C)
Adenomyosis (AUB-A)	**O**vulatory dysfunction (AUB-O)
Leiomyoma (AUB-L)	**E**ndometrial (AUB-E)
Submucosal myoma (AUB-L_0)	
Other myoma (AUB-L_0)	
Malignancy and hyperplasia (AUB-M)	**I**atrogenic (AUB-I)
	Not yet classified (AUB-N)

(Table 2) should be applied to describe the cause of the patient's abnormal uterine bleeding (AUB) (Munro et al. 2011). Each of the letters in the PALM-portion of the PALM-COIEN mnemonic represents a structural (or anatomic) abnormality. These abnormalities are identified most frequently by pelvic exam, radiographic imaging, and/or biopsy. They include the following:

- Polyps can be reported on biopsy or visualized as endometrial thickening on ultrasound, but are better characterized with sonohysterography or hysteroscopy.
- Adenomyosis can be clinically suspected when a woman complains of heavy/prolonged bleeding with increased cramping and deep thrust dyspareunia just prior to menses. Palpation of the uterus at the time can reveal a globular texture to the uterus and uterine tenderness. Adenomyosis is usually best visualized on magnetic resonance imaging (MRI), although newer 3D ultrasonography can be used.
- Leiomyoma can be suspected on bimanual examination if the uterus is firm and possibly enlarged and the contour is irregular. Leiomyomas are characterized by their position (intramural, submucosa, or subserosal) and size. Ultrasound can be used to identify leiomyoma, but MRI is more accurate at determining the location and volume of each lesion and may be the preferred test if the woman is considering embolization or myomectomy.

- Malignancy category includes all endometrial histological abnormalities from simple hyperplasia to premalignancies (endometrial intraepithelial neoplasia) to endometrial carcinoma (Munro et al. 2011). Endometrial biopsy is not routinely needed for low-risk women, but ACOG recommends biopsies for women with explained abnormal uterine if they have risk factors (ACOG Practice Bulletin No. 128, 2012). One large-scale retrospective study of over 1,500 women who underwent endometrial aspiration found that for women under 40 without obesity or diabetes, there was only a 1.1% chance endometrial sampling that would reveal evidence of significant (premalignant or malignant) disease (Nelson et al. 2016). Clinical judgment must be applied to sort out incidental noncontributing finding (such as a 1 cm intramural fibroid) from real causes for excessive bleeding.

The COIEN portion of the mnemonic represents functional or nonstructural etiologies. These include multiple gynecologic problems and non-gynecologic systemic diseases:

- Coagulopathies may be genetic (von Willebrand or excessive fibrinolytic activities) or acquired (platelet activation disorders) or result from severe sepsis or acute blood loss.
- Ovulatory dysfunction can result from genetic (amenorrhea of Turner syndrome), endocrinologic (androgen excess, thyroid dysfunction) or gynecologic (perimenopause) causes.
- Iatrogenic causes may be obvious (anticoagulants, copper IUDs) or more subtle (antihypertensive and antidepressant agents that affect dopamine production).
- Endometrial causes include functional abnormalities such as abnormal prostaglandin production, prostaglandin receptor imbalance, inappropriate activation of matrix metalloproteinases, or disruption of their tissue inhibitors.
- Not otherwise specified is self-explanatory.

The following sections will describe the most common bleeding abnormalities in adult premenopausal women and appropriate evaluation and recommended individualized treatments.

2 Secondary Amenorrhea

Secondary amenorrhea is defined in normally cycling women as the absence of any uterine bleeding or spotting for three consecutive cycles or, in women with baseline infrequent bleeding, as the absence of bleeding or spotting for two times their usual cycle length, but no longer than 6 months (Klein and Poth 2013). Secondary amenorrhea affects approximately 3–4% of reproductive-aged women. Pregnancy and lactational amenorrhea must always be excluded. Generally, amenorrhea is not considered to be a clinical problem when it is the desired result of therapy (e.g., endometrial ablation or progestin-only contraceptives). However, unexplained secondary amenorrhea can be concerning for a woman who has not completed her family and when it results from other health problems (e.g., renal failure, thyroid dysfunction). If the underlying cause for the woman's amenorrhea results in a lack of estrogen, secondary amenorrhea also presents concerns for long-term health risks associated with hypoestrogenemia – such as osteoporosis, dyslipidemia, and genitourinary problems. If the amenorrhea results from a lack of ovulation, then risks from unopposed estrogen (endometrial hyperplasia and cancer) must be addressed.

Secondary amenorrhea results from many different causes (Cox and Liu 2014). A complete history can help direct the work-up. Recent history of cervical procedures, such as LEEP or cone biopsy, suggests cervical stenosis, particularly if the woman continues to complain of monthly pelvic cramping. History of a dilation and curettage, especially in the face of infection, should lead to a work-up for Asherman's syndrome. A history of hemorrhage at delivery and a subsequent inability to breastfeed should raise concerns for Sheehan syndrome. Vasomotor symptoms and night sweats

suggest perimenopausal hormonal changes. New onset severe acne or hirsutism can indicate an androgen-producing tumor in a woman of any age or adult onset (atypical) adrenal hyperplasia in a young woman. Headache or visual changes with spontaneous galactorrhea suggest pituitary tumor. Recent dramatic weight changes and/or excessive exercise or extreme stress often precipitates functional hypothalamic amenorrhea. Asian or Arab ethnicity can prompt an evaluation for beta-thalassemia. Other medical problems such as thyroid dysfunction, sarcoidosis, lymphoma, renal failure, and those listed on Table 3 need to be considered. Medication history in Table 4 can be very informative for both current drugs and prior use (e.g., chemotherapy, especially with cyclophosphamide, methotrexate, 5-flourouracil, and vismodegib). A history of prior infrequent menses is helpful since gradual changes in bleeding patterns suggest a different set of etiologies than does an abrupt cassation of menses.

A comprehensive physical examination is needed. Short stature with wide carrying angle suggests Turner syndrome. Skin changes can provide clues. Hirsutism, male pattern balding, or acne are consistent with excessive androgen production or sensitivity, while acanthosis nigricans is an indication of insulin resistance. A malar facial rash raises the possibility of systemic lupus erythematosus. Striae, buffalo hump, and central obesity point to Cushing syndrome. Obesity by itself is more likely to cause infrequent, heavy bleeding, but in the extreme, a woman's bleeding may become so infrequent that technically the woman meets the definition of amenorrhea. Signs of genital atrophy support the diagnosis of estrogen deficiency. An enlarged, boggy, tender uterus is consistent with hematometra from cervical stenosis.

Laboratory testing should be guided by the findings from the history and physical examination. For example, a thyroid-stimulating hormone (TSH) test should be ordered. For a woman with fatigue, hair loss, weight gain, and delayed reflexes, severe hypothyroidism is more likely a cause of amenorrhea than other thyroid dysfunctions (Klein and Poth 2013).

Table 3 Secondary amenorrhea: conditions to consider

Anatomic defects
Asherman's syndrome (intrauterine synechiae, tuberculosis)
Cervical stenosis (iatrogenic)
Hypogonadism
Turner syndrome
Mosaicism
Premature ovarian insufficiency
Idiopathic
Injury: chemotherapy, radiation, mumps oophoritis, surgery
Hypothalamic causes
Excessive stress, extreme exercise, weight loss, eating disorders, pseudocyesis
Infection: TB, syphilis, encephalitis, sarcoidosis, neurotoxoplasmosis, AIDs
Chronic debilitating disease: wasting diseases (renal failure, hepatic failure, etc.)
Tumors: craniopharyngioma, germinoma, etc.
Traumatic brain injury
Pituitary causes
Tumors: hormone-secreting tumors (prolactin, ACTH, TSH, GH, etc.)
Empty sella
Necrosis – Sheehan syndrome: panhypopituitarism
Endocrine gland disorders
Autoimmune polyendocrine syndrome
Adrenal: adult onset (nonclassical) adrenal hyperplasia, Cushing syndrome, tumors
Thyroid myxedema
Ovarian tumors
Granulosa-theca cell, Sertoli-Leydig, thecoma, Brenner, cystic teratoma, cystadenoma, metastatic carcinoma, etc.
Uterine
Asherman syndrome (deliberate ablation; complication of infected dilation and curettage)
Receptor deficiency
Inflammatory/inflammation
Sarcoidosis, hemochromatosis
Other medical problems
Beta-thalassemia
Systemic lupus erythematosus
Rheumatoid arthritis
Myasthenia gravis
Dry eye syndrome
Malabsorption
Lymphoma
Histiocytosis
Clotting abnormalities

Table 4 Medications that decrease menstrual blood loss

Antidepressants
Antihistamines
Antihypertensives
Antipsychotics
Opiates
Cocaine

For women with no obvious etiology, the American Society of Reproductive Medicine (ASRM) recommends that once pregnancy and other obvious causes of amenorrhea have been ruled out, the work-up should start with TSH, follicle stimulating hormone (FSH) and prolactin levels (Practice Committee of ASRM 2008, pp. S219–25).

If TSH is abnormal, targeted therapies should be initiated to normalize thyroid function; endometrial protection should be provided until that goal is achieved. If prolactin is moderately elevated in the face of normal TSH levels, then a recreational drug/medication history may reveal the cause. If prolactin levels are greater than 70 mcg/mL, imaging (generally MRI) is needed to determine if there is a tumor of the anterior pituitary or an empty sella. If FSH is elevated, then additional hormonal testing (with repeat FSH, estradiol, and luteinizing hormone (LH) levels) is needed at least 1 month later to confirm the diagnosis of primary ovarian insufficiency with premature ovarian insufficiency (POI) (Cox and Liu 2014). If POI is diagnosed [high FSH, low estradiol] in the woman younger than age 30, karyotyping should be obtained because 13% of such women have abnormal karyotypes (ACOG. Committee Opinion No. 605 2014). Possible abnormalities include sex chromosome translocation and occult Y chromosome (which pose risks for gonadal tumors), fragile X syndrome, galactose-1-phosphate uridylytransferase (GALT) gene, FSH receptor genes, and other genes that may be clinically relevant to the woman and/or her children. If the woman with POI is over age 30, but younger than 40 years, she needs to be tested for autoantibodies associated with multiple endocrinopathies. If her amenorrhea has been caused by autoantibodies, she will need to be monitored over time for related endocrine failures, such as failure of her adrenal cortex, parathyroid, thyroid, and pancreas. POI may also result from chemotherapy (especially with alkylating agents or procarbazine) or radiation therapy (ACOG. Committee Opinion No. 605 2014).

If the FSH levels are normal or low, both PCOS and hypothalamic amenorrhea need to be ruled out. PCOS is discussed in detail in another chapter and summarized below. Hypothalamic amenorrhea is a diagnosis of exclusion when FSH and estradiol are low normal or low, but should be strongly suspected in the presence of low energy availability (with or without disordered eating), underweight, excessive exercise (athletic triad), or extreme psychological stress (Javed et al. 2013).

A progestin challenge test has been recommended in the past to distinguish between anovulatory etiologies (e.g., inadequate progestin) and those that cause estrogen deficiency (e.g., premature ovarian insufficiency). Today, it is recognized that the rates of both false positivity and false negativity with this test are excessive and that it should **not** be used as a diagnostic test. At best, progestin challenge test can help substantiate the diagnosis made by other tests; at worse it can lead to misdiagnosis. However, even though administration of progestin (daily treatment with MPA 10 mg or NETA 5 mg for 10–14 days) is not a diagnostic test, it may be very useful in terminating unopposed estrogen stimulation of the endometrium and should usually be administered while the diagnostic tests listed above are being processed.

The initial objective in treating women with amenorrhea is to correct any underlying abnormality; for example, suppression of prolactin production, correction of thyroid dysfunction, or surgical excision of androgen-producing tumor can restore normal hypothalamic-pituitary-ovarian (HPO) axis function. Lifestyle changes

including normalization of weight and moderation in exercise and stress management and cognitive behavior therapy can often provide long-term relief (Harrington et al. 2015). With chronic uncorrectable dysfunctions, hormonal balance must also be provided. For women with anovulatory cycles, at a minimum, periodic progestin therapy is needed. Those with estrogen deficiency need to have both estrogen and progestin restored. Higher doses that the typical doses used in menopausal women are necessary to prevent loss in these younger women with higher basal metabolic rates. Younger reproductive-aged women often prefer to use hormonal contraceptives in lieu of menopausal therapies. Addition of testosterone may be an effective adjunct for bone and muscle mass protection in women with POI if appropriate products are available. Measures to reduce cardiovascular risks must also be undertaken (Meczekalski et al. 2014). Contraception may also be important for women with premature ovarian insufficiency caused by autoantibodies, because nearly a quarter will show resumption of ovulation and 5–10% will spontaneously conceive if they rely on their ovarian insufficiency for birth control.

3 Infrequent Menses

Menstrual disorders are on a continuum. Many of the causes of amenorrhea described above can, in milder forms, cause infrequent bleeding. Some of the more common causes for infrequent bleeding include PCOS, prolactin disorders, thyroid dysfunction, and, less commonly, adrenal dysfunction. Abdominal fat accumulation represented by waist circumference is associated with infrequent bleeding in over 20% of women with simple obesity (De Pergola et al. 2009). Diabetes mellitus type 1 and type 2 are associated with infrequent menses; improved glycemic control improves cycling (Livshits and Seidman 2009). Infrequent bleeding can also be induced by drugs, such as dopaminergic, centrally-acting drugs and progestin treatments as well as by androgens (see Table 3).

Evaluation of a woman with infrequent bleeding proceeds much as outlined in the secondary amenorrhea section above with careful attention to elements in the history and physical examination that could point to the more easily recognizable causes. Initial laboratory testing is also similar. Lifelong infrequent menses may have different etiologies than new onset of infrequent bleeding. In a woman with no other etiology (thyroid dysfunction, androgen excess, etc.), matching her menstrual history and her weight over time can help confirm obesity-related dysfunction of the hypothalamic-pituitary-ovarian axis:

- Weight loss of only 5–10% using diet and exercise or bariatric surgery can often restore normal cycling and fertility – often at weights much higher than those at which the woman lost cycling during weight gain. This is important because some women rely on their weight-related amenorrhea for contraception and may experience unintended pregnancies after relatively slight weight loss.

A history of spontaneous galactorrhea should be investigated with serum prolactin levels. A scant amount of expressible galactorrhea is unlikely to affect menses, especially in women who have previously breastfed; routine testing of these women is rarely productive unless the woman is experiencing infertility.

A woman with infrequent menses should be asked about a history of any of the conditions listed in Table 3, since her current infrequent menses may lead to amenorrhea with time or with worsening of her condition. Lifestyle issues may be very telling especially for women who have eating disorders, exercise extensively, or experience other stress. Once again, therapy should be targeted to the underlying cause, but endometrial protection and protection from unintended pregnancy must also be included in treatment plans.

Polycystic ovary syndrome (PCOS) is a syndrome that includes a broad variety of manifestations of ovarian dysfunction that may include

menstrual irregularities, signs of androgen excess, and obesity. In addition to infertility, PCOS*See* Polycystic ovary syndrome (PCOS) is sometimes associated with acne, weight gain, hirsutism, thinning scalp hair, and higher lifetime risks for type 2 diabetes, high cholesterol, hypertension, and endometrial carcinoma. In 2004, the Rotterdam polycystic ovary syndrome consensus workshop codified guidelines for the diagnosis and management of PCOS. To be diagnosed with PCOS by the Rotterdam criteria, a woman must have at least two of the three criteria listed below and other conditions with similar signs, such as androgen-secreting tumors or Cushing's syndrome must be excluded (Rotterdam 2004). These three criteria include:

- Chronic anovulation (<8 menses per year)
- Hyperandrogenism (acne, hirsutism, temporal balding) or hyperandrogenemia
- Enlarged ovaries with at least 12 preantral follicles in each ovary (polycystic appearing ovaries (PAO))

The Rotterdam criteria created a definitional challenge because the third combination (criteria 1 and 3) is a meaningless tautology – all conditions causing chronic anovulation will induce polycystic appearing ovaries on ultrasound; many of these conditions have no relationship to androgen excess and are oftentimes found in young prepubertal girls, normally cycling women, oral contraceptive users, etc. To deal with these obvious definitional flaws, PCOS is being divided into subgroups based on different phenotypes. Each of these PCOS phenotypes has a different clinical presentation and different short- and long-term metabolic health risks that range from negligible to significant risks for cardiovascular disease and diabetes (Lizneva et al. 2016). The phenotype with the greatest long-term health risk is the group that meets all three of the Rotterdam criteria (Jovanovic et al. 2010).

The diagnosis of PCOS is predominantly a clinical one:

- History usually reveals a lifelong pattern of infrequent menses. However, some women develop "PCOS" later in life following significant weight gain. Anovulation can be suspected when women report no moliminal symptoms; they have no complaints of bloating, cramping, or other symptoms just prior to menses. In higher androgen states, menstrual flow is generally lighter. History of gestational diabetes is not uncommon.
- On examination, blood pressure, height, weight (BMI) and waist circumference should be measured. The presence of acne, hirsutism, androgenic balding, breast changes, and acanthosis nigricans is also suggestive.
- Laboratory testing is used to rule out other etiologies, not to diagnose PCOS. Gonadotropin levels are helpful only if history suggests premature ovarian insufficiency. Testosterone levels are generally ordered in practice to rule out tumors (total testosterone is quite adequate) and in research to monitor therapeutic response (free testosterone is often recommended despite its high cost and usual inconsistent results). Interestingly, today many experts now argue that testosterone levels are not necessary and may misclassify women if hyperandrogenism has been detected on physical exam (Tosi et al. 2016). DHEAs levels are usually not recommended in first-line evaluation, but can be useful for a markedly hirsute woman with normal testosterone levels. In woman under age 25 with hirsutism (especially rapidly progressive hirsutism), measurement of 17-hydroxy progesterone levels is indicated to rule out adult onset (atypical) adrenal hyperplasia. TSH may be appropriate if other symptoms or signs suggest thyroid dysfunction. Prolactin is routinely needed when spontaneous galactorrhea is found and when the woman is seeking pregnancy. Tests for insulin resistance are not part of the work-up and are not helpful. However, glucose tolerance tests may be appropriate for woman's general health, especially in women with risk factors for diabetes. Similarly, fasting lipid panels may be

clinically indicated to assess the woman's risk factor for cardiovascular disease (metabolic syndrome) for some PCOS phenotypes, such as obese women with androgen excess, but they are not needed to make the initial diagnoses of PCOS. Women with PCOS should be screened for mood disorders (especially depression) because those problems are more frequently found among women with this syndrome.

The goals of therapy for PCOS include reduction in the production and circulating levels of androgens, protection of the endometrium from unopposed estrogen, achievement of normal body weight, planning and preparing for pregnancy, and, where indicated, lowering of the risks for cardiovascular disease and diabetes. Treatment again focuses on correcting any identified problems. The goal may not be to restore cyclic monthly bleeding, especially if the woman appreciates the convenience of infrequent bleeding episodes; endometrial suppression is quite sufficient. Other interventions depend upon the woman's presenting symptoms and short-term childbearing plans. Usually lifelong, healthy lifestyles (especially weight loss and exercise) are strongly encouraged because excessive weight is often a problem and weight loss can be very challenging in women with "thrifty" PCOS metabolism. Selection of a diet comes down to finding a healthy diet that the woman can follow long term:

- Intriguingly, orlistat 120 mg given three times a day resulted in greater weight loss than metformin and reduced testosterone levels as well.
- In early experiments, lipid-lowering drugs have proven to be effective in reducing androgen excess and insulin resistance; however, more clinical work is needed before this therapy can be endorsed.

Various treatments for hyperandrogenism are available, generally involving estrogen-containing contraceptives with possible addition of an antiandrogen, such as spironolactone. Metformin is not generally recommended unless the woman has other indications, such as prediabetes. In fact, metformin is not considered to be first-line therapy, even when treating for women with PCOS for infertility (ACOG Practice Bulletin 108 2009; Legro et al. 2013).

4 Postcoital Bleeding

History is critical in identifying this bleeding abnormality. The two most common causes of postcoital bleeding are neoplasia (cervical polyps, cervical ectropion, cervical carcinoma) and cervical infection (chlamydia, gonorrhea, herpes simplex, trichomoniasis), but other causes, such as trauma and foreign bodies, must be considered (Tarney and Han 2014).While asymptomatic cervical polyps do not need to be removed, those that cause bleeding may harbor significant disease and warrant histological evaluation (Nelson et al. 2015).

5 Intermenstrual Bleeding

Spontaneous bleeding between menses is concerning for pregnancy and pregnancy complications in young women. In nonpregnant women, it can indicate endometrial disease, including malignancy. Occasionally, tubal carcinoma presents with chronic pink, watery vaginal discharge. Granulosa cell ovarian tumors can induce endometrial hyperplasia. Endometritis and more generalized pelvic infection are also classically listed as causes of intermenstrual bleeding, but usually women with these infections present with complaints of pain or discharge. Frequently in younger women, intermenstrual bleeding is iatrogenic – due to missed contraceptive pills, progestin-induced endometrial changes from intrauterine devices, implants, or injections – and does not need evaluation. Reassurance and treatment with nonsteroidal anti-inflammatory agents or antifibrinolytic agents may help reduce the number of episodes and shorten the remaining ones.

Unexplained intermenstrual bleeding, especially in women with risk factors for endometrial disease, requires evaluation of the endometrium. These risk factors include age (>45 years) and unopposed estrogen exposure (obesity, anovulatory cycling) (ACOG Practice Bulletin No. 128 2012).

Usually an office biopsy can provide the diagnosis (endometrial hyperplasia), but if the patient does not respond to therapy targeted to that diagnosis (e.g., progestin), she would need further work-up with either sonohysterography or hysteroscopically directed biopsy. If hyperplasia is diagnosed, the LNG-IUS 20 mg/24 h has been shown to be the most effective treatment (Gallos et al. 2010). Long-term therapy is needed because of the high rate of recurrence and progression to endometrial carcinoma.

6 Heavy Menstrual Bleeding

Nearly one in seven women reports having experienced heavy menstrual bleeding (HMB) at some point. Historically, heavy bleeding was defined as loss of more than 80 mL of blood each cycle because blood loss less than that amount did not result in anemia (Hallberg et al. 1966). HMB can lead to serious, even life-threatening anemia (Nelson and Ritchie 2015). It negatively impacts on a woman's quality of life and on her productivity. A classic analysis done over a decade ago estimated that women with HMB earn $1,692 less income each year. In addition, the cost of sanitary protections can be considerable. Women with HMB also utilize medical services at much higher rates than women with normal menses.

Accurate quantification of blood loss may be difficult in the clinical setting. In part, this may be because only 40–60% of total menstrual flow is made up of blood. In addition, differences in the absorbency and size of different sanitary protection products and variations in the fastidiousness and habits of individual women make it difficult to interpret the history. Symptoms of fatigue or dizziness may help support the diagnosis of resultant anemia.

Perception of normalcy often influences women's characterization of their flow. On the one hand, in Hallberg's study, nearly half of women who did have heavy losses (>80 mL) characterized their monthly flow as light or moderate and did not recognize that their loss was excessive. Prolonged bleeding is more easily diagnosed probably because it is more easily quantified than heavy blood loss. Surprisingly, many women who routinely have menstrual flow for more than 8 days frequently report it as "normal," often because many or all of the women in their families had similar bleeding patterns. Some women may think heavy or prolonged blood loss indicates higher fertility or femininity or more through "cleaning out" (Coutinho and Segal 1999). On the other hand, some women overestimate their losses. In Hallberg's classic study, over 30% of women who lost 20–40 mL of objectively measured blood characterized their bleeding as "heavy" (Hallberg et al. 1966). Fortunately, today the definition of HMB has been expanded to include women who lose less than an average 80 mL each cycle, but report their flow is heavy enough to interfere with their functioning. Sometimes this represents occasional heavy cycles, and sometimes it results from a short term (hours) of heavy bleeding during every cycle. Women in this group may not need extensive work-ups, but they certainly can be offered treatments that can reduce their bleeding. However, there are instances when a woman's blood loss may not meet the definitional threshold, but it is distinctly greater than losses she has experienced in the past. This may be an indication of new pathology and needs attention.

On physical examination, signs of anemia should be sought, such as pale conjunctiva or tachycardia. Examination should rule out obvious non-uterine sources of blood lose (large hemorrhoids). Iron deficiency anemia in a woman with a normal diet substantiates a woman's claim of excessive blood loss, but it may be necessary to

perform the hemoglobin testing at the end of menses that can detect their anemia.

Heavy menstrual bleeding is generally divided into two categories: acute excessive bleeding and chronic heavy menstrual bleeding.

Table 5 Medications that increase menstrual blood loss

Anticoagulants: warfarin, heparin
Antiepileptic agents: Dilantin, phenobarbital
Digitalis
Nonsteroidal anti-inflammatory drugs, including ASA
Contraceptives: copper IUD, steroidal hormones
Herbal agents: ginkgo, ginseng, motherwort

6.1 Acute Heavy Bleeding

Hemodynamic stability must be quickly evaluated by symptoms and vital signs in women who present with acute heavy uterine bleeding. Acute rapid blood loss, even at higher levels of hemoglobin, is not as well tolerated as slow, chronic losses. Pregnancy tests and rapid point-of-care hemoglobin tests are needed to direct further actions.

Women who are not stable or who have signs of hypovolemia should receive fluids through large-bore IVs and blood transfusion with appropriate clotting factor replacement. A rapid abbreviated history should be conducted that includes information about the current bleeding episode (duration, flow, pain, and associated symptoms such as headache, palpitations, shortness of breath, dizziness, fatigue, pica, and past episodes (when, what diagnoses, what therapies) as well as any relevant medical problems that may cause losses (bleeding disorders, acute leukemia, immune thrombophilia purpura, aplastic anemia) and those be adversely impacted by anemia (diabetes, hypertension, cardiac disease). Recent surgical procedures (e.g., endometrial, cervical, or other uterine) should also be documented. Examination should first confirm that the source of the bleeding is uterine. Quick laboratory testing should include complete blood count, blood type and partial thromboplastin time, prothrombin time, activated partial thromboplastin, and fibrinogen. After the woman has been stabilized, evaluation should proceed as outlined below to arrest her bleeding, establish its etiology, and prevent future episodes.

For women without life-threatening acute blood loss and those who have been stabilized, a more expanded history is needed. Details of the current episode of bleeding and any related symptoms should be expanded to include the past menstrual history and obstetrical and gynecology history. Information about medication use can be helpful especially if it contributes to bleeding (anticoagulants) or induces anovulation and unopposed estrogen (see Table 5). The woman should also be asked about any previous treatments she has been given to treat heavy bleeding. Family history of coagulation or thromboembolic disorders and any contraindication to medication usually used to treat HMB should be identified.

Physical examination should focus on physical findings suggestive of anemia, systemic disease (hepatic or renal failure, sepsis or hematopoietic cancers), endocrine disorders (thyroid), coagulopathy (bruising), and pelvic abnormalities (masses, evidence of trauma, or cervical or vaginal abnormalities that could account for the bleeding) (see Table 5).

Laboratory testing should be guided by the findings from the woman's history and physical examination. Thyroid-stimulating hormone, liver function tests, renal function tests, cervical infection tests, and iron reserve tests (serum iron, total iron binding capacity, and ferritin) may each provide important information for different clinical presentations.

Imaging tests (especially ultrasound and saline infusion sonography) may be helpful at some point to assess the PALM structural causes (see above).

Endometrial sampling to rule out endometrial disease should be performed after the woman is stabilized in reproductive-aged women over 45 years and in younger women with a history of unopposed estrogen or a history of failed medical management of abnormal bleeding (ACOG Practice Bulletin 128 2012).

Most women with acute excessive bleeding will respond rather rapidly to appropriate medical

therapy. However, in some cases, emergent surgical treatments may be required, especially if trauma is suspected. The procedures vary. Dilation and curettage may be needed to halt bleeding from retained products of conception or bleeding polyps; myomectomy is needed for an aborting fibroid; surgical repair may be needed for trauma. Emergency hysterectomy can be lifesaving in certain cases.

Medical therapy recommendations for acute bleeding have undergone evolution:

- Classically high-dose estrogen therapy has been recommended to be used to halt acute excessive bleeding. Intravenous conjugated equine estrogen is specifically approved by the US Food and Drug Administration for treatment of acute abnormal uterine bleeding (ACOG Committee Opinion 557 2013). Dosing regimens include 25 mg CEE IV every 4 h for unstable patients or 2.5 mg CEE orally every 4–6 h for 14–21 days for hemodynamically stable women. Progestin is generally added (MPA 5 mg once or twice a day) to support the endometrium 12–24 h after initiation of estrogen (when bleeding slows) and is continued until estrogen therapy is terminated. This approach mimicked the processes seen in the normal menstrual cycle. However, the only randomized, prospective, placebo-controlled study for a high-dose estrogen was a 5-h trial in which 17 women were given high-dose conjugated estrogen therapy and 17 received saline in an ER setting (DeVore et al. 1982). Intravenous estrogen is still the most common treatment prescribed for women who require hospitalization for transfusion and stabilization. However, women with iron deficiency anemia can often have reactive thrombocytosis This reactive thrombocytosis places the woman at higher risk for deep venous thrombosis and pulmonary embolism (Nelson and Ritchie 2015). Addition of high-dose estrogen increases that risk factor. However, progestin-only therapies outlined below have not been tested in the setting of acute bleeding.
- For outpatient therapy, high-dose estrogen-containing oral contraceptives have been the mainstay of therapy for decades, despite the fact that there is little in the literature to support any of the classically recommended regimens. Over time, the dose used in those regimens has been reduced to minimize the risk of thrombosis. The initial regimens popularized in textbooks called for 50 mcg ethinyl estradiol/30 mcg norgestrel oral contraceptives to be taken four times a day for 5 days (essentially a pill pack). Later regimens called for twice daily dosing for 5 days. Most recently, the recommendation is that two tablets of a 1/35 formulation be given the first day followed by one pill a day until the pill pack is finished (Fritz and Speroff 2011).
- In the largest randomized, comparative clinical trial for outpatient treatment of acute excessive uterine bleeding, Munro et al. demonstrated that medroxyprogesterone acetate (MPA) 20 mg taken orally three times a day for 7 days followed by MPA 20 mg taken once daily for an additional 21 days was at least as effective as high-dose oral contraceptives (one tablet 1/35 oral contraceptive taken three times a week for 7 days followed by any 1/20 formulation taken one tablet a day for 21 more days) in stopping bleeding, in avoiding surgery, and in achieving patient satisfaction (Munro et al. 2006). Although Munro's patients were all hemodynamically stable and treated as outpatients, the ACOG Committee Opinion on the topic does not restrict the use of this progestin-only therapy to outpatients (ACOG Committee Opinion 557 2013). The fact that progestin-only approaches avoid VTE risk makes this their used first-line treatment option.

Medroxyprogesterone acetate (MPA) 20 mg taken orally three times a day for 7 days followed by MPA 20 mg once daily for an additional 21 days is a safe and effective treatment to stop acute bleeding with a wide range of endometrial pathology.

Some authorities have recommended using progestin when the endometrial lining is

thickened and estrogen treatments when it appears to be atrophic. This recommendation assumes the clinician has access to imaging equipment, which may not be true in many settings. Furthermore, the imaging can add extra cost. Fortunately, in the largest prospective trial of management of acute bleeding in patients eligible for outpatient therapy, progestin-only therapy was very effective in all women. Bleeding was stopped in women with biopsy-proven atrophy as well as those whose endometrial sample revealed endometrial hyperplasia (Ammerman and Nelson 2013).

Once the acute bleeding has been arrested, it is important to ensure that future episodes are prevented. This can usually be achieved using therapies outlined for treatment of chronic heavy menstrual bleeding below.

6.2 Chronic Heavy Menstrual Bleeding

The goals of the work-up of heavy menstrual bleeding are to establish whether the heavy bleeding is due to a treatable organic disorder and whether the bleeding is ovulatory or anovulatory and to assess the burden the woman's symptoms place on her.

The history includes all the items described in the acute HMB section above. Iatrogenic causes, especially medications, need to be thoroughly evaluated (see Table 5). Serious medical conditions can also present with new onset or chronic heavy menstrual bleeding. Women who have renal insufficiency approaching anuria experience very heavy bleeding. Once renal failure is complete, these women become amenorrheic. However, after dialysis is started, they again may experience very heavy menses. These losses are very significant, because the woman has no ability to stimulate production of red blood cells with erythropoietin. With loss of vitamin K in hepatic failure (liver cirrhosis or active hepatitis), women can develop heavy menses. Hypersplenism and adrenal hyperplasia can also cause HMB. As noted earlier, endocrine abnormalities (thyroid myxedema) can induce heavy bleeding. For women with hematopoietic carcinoma, heavy bleeding can be their first symptom.

Physical examination would include vital signs (including BMI); thyroid exam; tests for abdominal tenderness, hepatomegaly or abdominal distention, striae, skin bruising, petechiae, and pallor; and pelvic exam. Imaging studies can be selected based on the woman's history, and exam findings to define any structural/anatomic causes (PALM) as described above.

The function causes (COIEN) summarized above must also be evaluated.

In recent years, there has been a growing awareness that coagulopathies are very common in women of any age. Whenever other etiologies are not identified, it is necessary to evaluate the ability of the woman to form clots and to maintain them. Some bleeding disorders are classically genetic (von Willebrand disease, some forms of thrombocytopenia), but many are acquired. Inherited bleeding disorders are found in 10–20% of adult women with objectively verified heavy menstrual bleeding. In one study of 115 women with idiopathic heavy menstrual bleeding, 47% were found to have a hemostatic abnormality, the most common of which was acquired platelet aggregation defects (44%). Platelet disorders can include abnormal numbers of platelets (ITP or leukemia) or disorders of platelet function (Philipp et al. 2005). In a subsequent study, bleeding disorders were found in 31% of women with HMB (average PBAC of 271) and platelet disorders accounted for 69% of those cases; von Willebrand was a distinct second at 22% (Knol et al. 2013). Philipp et al. have developed a detailed screening tool to detect bleeding disorders in women with heavy menstrual bleeding (Philipp et al. 2011). This diagnosis is often overlooked; in a survey of over 500 OB-GYNs, only 38.8% said that they would consider bleeding disorders for adult women with HMB:

- ACOG recommends screening for an underlying disorder of hemostasis in an adult woman if she has had heavy menstrual bleeding since menarche, and she has experienced excessive blood loss postpartum, with surgery or with

dental work, and she has had at least two of the following conditions: nose bleeds one to two times per month, frequent gum bleeding, and family history of bleeding symptoms (ACOG Adolescent Committee Opinion 580 2013). The initial work-up recommended is a CBC with platelet count, PT, PTT, and possible fibrinogen. Specific tests for von Willebrand are also listed; either ristocetin cofactor assay or antigen testing is generally recommended as screening test. Specific von Willebrand defects require more detailed testing, usually best done by hematologist [x ref. Committee Opinion 580].

Ovulatory dysfunction is one of the most easily diagnosed conditions. Usually a menstrual history is sufficient, but hormonal testing can be helpful in identifying medical conditions underlying the menstrual disorder (see above). Anovulatory bleeding can be heavy for several reasons involving the endometrial environment. Unopposed estrogen stimulation induces thicker endometrial layer; endometrial sloughing is dyssynchronous and, therefore, prolonged. Without ovulation, the levels of $PGF_{2\alpha}$ responsible for vasoconstriction do not rise in the "luteal phase" to exceed the levels of PGE_2 responsible for vasodilation. Abnormalities can also occur in the balance in production of thromboxane (promotes platelet aggregation promotion) and prostacyclin (inhibits platelet aggregation). In ovulatory women with HMB, similar imbalances can be seen because of abnormal prostaglandin synthesis and/or increased numbers of receptors. Diagnosis of these problems has to be clinical; response to NSAIDs helps support the diagnosis.

Targeted therapies are needed to treat heavy menstrual bleeding due to systemic diseases. For example, excessive bleeding due to thyroid dysfunction requires only temporary menstrual suppression until euthyroidism can be restored. Endometrial polyps can be excised. Women with underlying disordered hemostasis will need targeted therapy with agents such as DDAVP (desmopressin acetate) as outlined in Management Guidelines from the National Health, Lung and Blood Institute. Treatment of endometrial hyperplasia is covered in other chapters. However, for a woman with chronic conditions, such as bleeding diatheses, hypersplenism, bone marrow suppression, as well as those with uterine abnormalities, such as leiomyoma or adenomyosis or idiopathic heavy menstrual bleeding, two questions need to be answered to determine her best treatment options:

- Is she seeking pregnancy?
- How excessive is her blood loss? (or how much of a reduction does she need?)

6.3 Medical Therapies for Chronic Heavy Menstrual Bleeding

For women seeking pregnancy and for women who need only slight reductions in their blood loss, nonhormonal methods may be offered. In this case, nonsteroidal anti-inflammatory agents (NSAIDs) taken at high enough doses at appropriate intervals reduce blood loss by 20–30% (Lethaby et al. 2013). One typical regimen is ibuprofen 800 mg orally every 8 h from onset of menses until end of heavy flow (up to 5 days). Antifibrinolytic agents can reduce blood loss about 40% (Freeman et al. 2011). A typical treatment would include Lysteda 650 mg, two tabs orally, three times a day starting at the onset of bleeding and continuing through the last day of heavy flow (but not more than 5 days). These agents have the advantages that they do not affect fertility and they are used only at the time of menses.

For women who are not seeking pregnancy, endometrial suppression can provide significant reductions in menstrual blood loss even though for many of them, such use would be off-label. Usually first-line therapy is medical [combined hormonal contraceptives, progestin-only pills, injectable progestin contraceptives, LNG-IUS-20 mg/day, cyclic oral progestin). Surgery should generally be reserved for those who have other pelvic pathology and those whose bleeding is not medically controlled (infra vide). Unfortunately, in a recent study of over 2,200 women who

underwent hysterectomy for benign conditions in 2013, over one-third of the cases had no documentation that any medical treatments had been used prior to surgery (Corona et al. 2015).

Hormonal contraceptives are the therapy most frequently prescribed to control heavy bleeding. Traditionally oral contraceptives, contraceptive patches, and contraceptive vaginal rings have been used cyclically to reduce the amount of scheduled bleeding by 50–70%. Extended cycle (AKA continuous) use of oral contraceptives or vaginal contraceptive rings has been shown to reduce endometrial thickness and to substantially reduce the total numbers of days of scheduled bleeding even further (Edelman et al. 2014). Extended use of the current transdermal patch is not recommended given the increasing estrogen levels associated with its prolonged use. One oral contraceptive pill has been approved by the FDA for treatment of heavy menstrual bleeding; the multiphasic desogestrel/estradiol valerate pill reduced heavy menstrual bleeding almost as well as the high dose LNG-IUS did in its pivotal clinical trial (Kaunitz et al. 2010; Wasiak et al. 2013).

Despite decades of clinical experience utilizing DMPA to achieve amenorrhea, there is very little in the literature about its use to treat heavy menstrual bleeding. There is evidence that DMPA is useful in preventing recurrent hemorrhagic ovarian cysts in women on chronic anticoagulation therapy, and DMPA was shown to reduce blood loss among 20 women with uterine fibroid-associated HMB. DMPA in conjunction with GNRH agonists has been helpful in treating women at risk for severe thrombocytopenia from myelosuppressive therapy for cancer. One recent review concluded that DMPA use was not contraindicated for use by women with inherited bleeding disorders. Although menstrual blood loss diminishes with longer-term contraceptive implant use, its unpredictable impact on bleeding discourages the use of the implant to treat HMB. GnRH agonists can be used short term to suppress estrogen protection and endometrial growth. Usually add-back therapy is used for longer-term use to reduce the associated estrogen deficiency symptoms and adverse reactions on bone health (Bradley and Gueye 2016).

The LNG-IUS-20mcg/24 h is the most effective medical therapy for idiopathic heavy menstrual bleeding (Bitzer et al. 2015; Lethaby et al. 2015). In the comparative open-label randomized trial against luteal phase MPA 10 mg per day, this LNG-IUS reduced blood loss by at least 50% and normalized blood loss to <80 mL in every episode in 85% of subjects (Kaunitz et al. 2010). Women with leiomyoma <4 cm which protruded into the endometrial cavity <50% of their diameter were included in the study. Subsequent studies have shown LNG-IUS superior to different medical comparators (NETA, tranexamic acid, mefenamic acid) for treatment of idiopathic HMB (Kiseli et al. 2016) and for HMB due to adenomyosis (Shaaban et al. 2015). Women who are on anticoagulant therapy also benefited from LNG-IUS-20 by increasing hemoglobin levels (Vilos et al. 2009). The ECLIPSE study found the LNG-IUS to be superior to other medical therapies, but only for the first 3 years (Gupta et al. 2015):

- The most recent Cochrane Review also concluded that compared to endometrial ablation, satisfaction rates and quality of life measures were similar, but the LNG-IUS was more cost-effective. Another advantage is that the LNG-IUS also provides contraceptive protection. This same review concluded that the LNG-IUS was less effective than hysterectomy in reducing HMB, but quality of life was improved by both. The LNG-IUS appears to be more cost-effective than hysterectomy for up to 10 years after treatment (Lethaby et al. 2015). This last point was substantiated in a 10-year study of women randomized to hysterectomy vs. LNG-IUS, which showed that over half of the women in the LNG-IUS arm avoided having that surgery.

Most recently ulipristal acetate 5 mg orally each day has been shown to rapidly and effectively control heavy menstrual bleeding preoperatively for women with leiomyoma (Donnez et al. 2014). Early clinical trials with ginger extracts

showed greater decrease in blood loss than was seen with placebo (Kashefi et al. 2015).

6.4 Surgical Therapies for Heavy Menstrual Bleeding

Surgical options are also available, but generally are reserved for situations when medical therapies are inappropriate or inadequate. For women with heavy menstrual bleeding, endometrial ablation scarifies the endometrial lining. Endometrial ablation techniques have diversified over time to provide flexibility and accommodate different endometrial configurations. Electrical or electrocautery ablation, hydrothermal ablation, balloon therapy, radio frequency, cryoablation, and microwave ablation techniques all have roughly equivalent efficacy and satisfaction rates (Angioni et al. 2016). Initially introduced as a less invasive surgical option, which could reduce hysterectomy rates, its use flourished. Success rates for amenorrhea/normalization of blood loss are reported to be 80% after one procedure; some will undergo a repeat ablation and about 10–15% of women ultimately undergo hysterectomy. Although there are infrequent procedure complications, there are two important caveats associated with ablation. First, the endometrium must be thoroughly assessed to rule out malignancy and premalignant conditions prior to ablation. Second, the woman must also be protected against pregnancy until menopause.

For women with limited numbers of leiomyoma causing their excessive bleeding, uterine artery embolization and myomectomy may be options. In a 10-year follow-up study of women randomized to embolization, two thirds avoided hysterectomy (de Bruijn et al. 2016). Laparoscopic myomectomy may be helpful in wishing to preserve fertility. Often women will need to have cesarean delivery following myomectomy, especially if the endometrial cavity is entered during the surgery.

Hysterectomy is a definitive treatment for heavy menstrual bleeding, but it can cause severe complications for a small minority of women (Marjoribanks et al. 2016). Less invasive surgical approaches (laparoscopy, robotic surgery) significantly reduce recovery time for women.

7 Conclusions

Uterine bleeding patterns are a primary vital sign of a woman's reproductive health. Abnormal uterine bleeding is most common at the extremes of reproductive life (puberty and perimenopause), which is discussed in other chapters. Abnormal bleeding patterns that manifest during the reproductive years warrant evaluation and usually therapy. The FIGO terminology should be used in each case to fully describe all the dimensions of the woman's bleeding (its frequency, duration, volume, and variation). The PALM-COEIN classification system for abnormal uterine bleeding provides a shorthand, uniform system of diagnosis that can improve visit-to-visit communications. The spectrum of abnormal uterine bleeding patterns includes both disorders of amounts (amenorrhea to heavy and prolonged bleeding) and timing disorders (postcoital, intermenstrual bleeding).

Infrequent bleeding and secondary amenorrhea can represent problems anywhere along the hypothalamic-pituitary-ovarian (HPO) axis, within the uterus, or the secondary effects of systemic disease or medications on that HPO axis. Work-up should be guided by the history and physical findings. Comprehensive broad-based evaluation strategies have been described that are very time efficient. However, they are often not cost-effective. Therapies should target the underlying cause, but should also normalize sex steroid levels and protect end organs (endometrium, bone) that are affected by those abnormalities.

Heavy bleeding can result in serious, even life-threatening anemia; more commonly it can significantly diminish a woman's quality of life and her productivity. Acute bleeding usually commands attention, but chronic excessive losses may not be appreciated as a health problem until anemia develops. Heavy bleeding can have structural causes (PALM) and/or functional causes (COEIN). Systemic disease and medications can impact on bleeding by directly impacting uterine and endometrial factors or by altering the function of the HPO axis. Attention first focuses on correcting the woman's underlying pathology,

but endometrial suppression, usually with hormonal contraceptives, NSAIDs, or tranexamic acid are first-line therapies. Both versions of the LNG-IUS-20 mg/24 h are also very effective, first-line therapies for idiopathic chronic HMB. Other hormonal methods, including DMPA or NETA suppression, offer alternatives that can be very effective when used as directed.

It is important to educate women about normal patterns of menstrual bleeding so they can help identify early abnormalities in their patterns that may represent significant pathologies. In this setting, clinicians should reassure women about the health benefits of endometrial suppression (iatrogenic amenorrhea) provided by progestin-only or extended cycle combined hormonal therapy. This apparent mixed messaging requires skill and time, but is very important to the long-term success of such therapies and to the health of patients.

Procedural therapies have also increased in popularity. Endometrial ablation is possible using a wide range of techniques. Uterine artery embolization may be very effective when dealing with HMB if only a few leiomyomas require treatment. Myomectomy is attractive to women wishing to preserve their fertility if bleeding is due to few myomas. Hysterectomy is reserved for women with pelvic pathology and for those who are not candidates for or do not respond to appropriate medical treatments. The potential role of newer agents, such as ulipristal acetate, is being explored.

8 Cross-References

► Workup and Management of Polycystic Ovary Syndrome

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