

## Chapter 26

# Normal and Abnormal Uterine Bleeding

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### DEFINITIONS

**Amenorrhea**—The absence of menstrual bleeding for more than 6 months.

**Breakthrough bleeding**—Intermenstrual bleeding that occurs despite the use of exogenous hormones.

**Dysmenorrhea**—Painful menstruation.

**Interval bleeding**—Bleeding between menstrual cycles.

**Menorrhagia**—Prolonged menstrual bleeding that is excessive in amount, duration, or both that occurs at regular intervals.

**Metrorrhagia**—Bleeding between periods.

**Oligomenorrhea**—Bleeding that occurs less frequently than every 35 days.

**Polymenorrhea**—Bleeding that occurs more often than every 21 days.

**Postmenopausal bleeding**—Uterine bleeding occurring more than 12 months after the last menstrual period of a menopausal woman.

**PALM-COEIN**—Polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified. The term *dysfunctional uterine bleeding (DUB)* is discouraged since the implementation of this classification system.

### INTRODUCTION

Abnormal uterine bleeding (AUB) is an extremely common gynecologic complaint. It is estimated that 30% of women experience menorrhagia annually. This debilitating condition is clinically important; Mahoney and colleagues report it is the indication for two thirds of hysterectomies and nearly 25% of gynecologic operations. Thus, the impact of this condition on the public health and health care costs is significant. Because medical therapies for AUB have significant failure rates or side effects, surgical treatment by hysterectomy remains a major therapeutic option for chronically symptomatic women. This chapter reviews normal menstruation, the pathophysiology underlying AUB, the evaluation of AUB, and current treatment modalities.

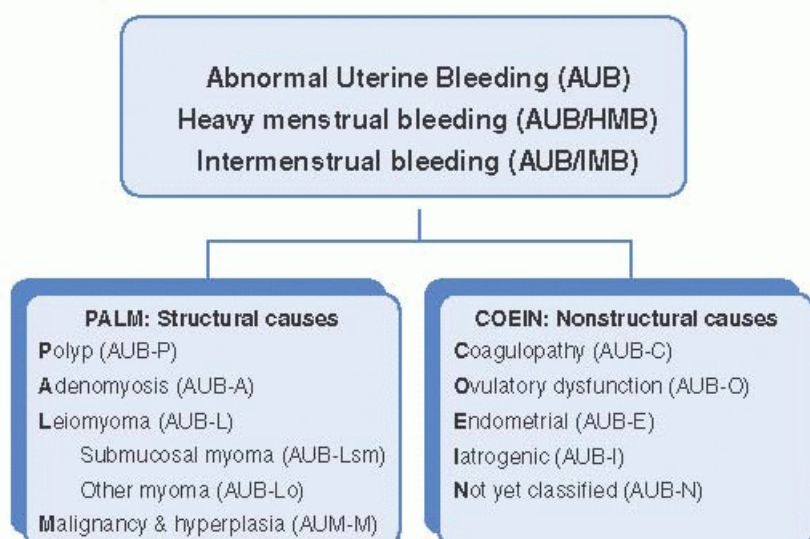
Reproductive capability in a young woman begins at the point of menarche, which is the beginning of cyclic uterine bleeding in the anatomically and physiologically normal female. Menarche marks the beginning of an important stage in a young woman's physical reproductive maturation and development. Attitudes toward menstruation, what is considered "normal," and the decision to seek medical evaluation are impacted by a variety of factors. In one cross-sectional US study of nearly 2,000 women, the authors concluded that Western cultures tend to "medicalize" menstruation, as evidenced by the media information that depicts menstruation as something that should be managed and remedied. This investigation also suggested that positive attitudes toward menstruation are

more prevalent among women with higher educational levels and higher incomes. Positive attitudes were more common among women who exercised frequently and older women who were approaching menopause. Race and ethnicity also played a role in attitudes toward menstruation with non-European Americans having a more positive attitude toward menstruation. Common wisdom would suggest, and studies support, the assumption that women who do not have an understanding of normal menstrual physiology are more likely to become alarmed about any disruption in what is perceived to be normal menstruation. As health care providers, it is our responsibility to educate our patients about what is normal and what symptoms would require medical evaluation. Current medical therapies are quite effective in the management of most of the disturbances of menstrual function that occur in the absence of infection, gestation, or uterine tumor. The success of these therapies depends on a complete understanding of normal menstrual physiology and of the effects of the various agents available for treatment. In addition, new surgical diagnostic and therapeutic technologies are becoming available to aid in the management of patients who fail to respond to conventional endocrine manipulation by medical therapies.

The normal interval between menstrual cycles is 21 to 35 days, and the normal duration is generally 5 days. Although heavy bleeding has been traditionally described as a blood loss exceeding 80 mL, a more practical approach is to rely upon the patient's perception. The term *menorrhagia* has been used to define heavy bleeding, while *metorrhagia* is used to define bleeding between periods. *Oligomenorrhea* is used to describe bleeding that occurs less frequently than every 35 days, and *polymenorrhea* is used to define bleeding that occurs more often than every 21 days.

In 2011, in an effort to standardize the nomenclature used to describe uterine bleeding abnormalities, a new classification system was introduced by the International Federation of Gynecology and Obstetrics (FIGO). The classification system known by the acronym **PALM-COEIN** (polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified) is also supported by the American Congress of Obstetricians and Gynecologists.

The PALM-COEIN system differs from the previously used nomenclature in that it categorizes uterine bleeding by etiology as well as bleeding pattern. Under the new classification system, terms such as menorrhagia would be replaced by heavy menstrual bleeding. The PALM-COEIN system also uses letter qualifiers to identify the etiology (**Fig. 26.1**). Prior to the implementation of the PALM-COEIN classification system, the term dysfunctional uterine bleeding (DUB) was often used interchangeably with AUB; DUB was used to indicate AUB for which there was no systemic or structural etiology. The use of the term DUB is not part of the PALM-COEIN system, and its use is discouraged by the FIGO Working Group in 2011.



## **MENSTRUAL PHYSIOLOGY**

Menstruation is the physiologic shedding of the endometrium associated with uterine bleeding that occurs at monthly intervals from menarche to menopause. In the years between these two physiologic landmarks, menstruation will occur 400 to 500 times in the average woman. According to the classical theory of the physiology of menstruation, it is the superficial functional layer of the endometrium that is shed during menstruation, and regeneration proceeds from the remaining intact basalis.

Recent work in humans has confirmed the presence of endometrial stem cells, which most likely are located in niches within the basalis layer. Additionally, it appears that these progenitor cells are hormonally independent. The proliferative potential of these cells is maintained in the noncycling state as demonstrated by their ability to regenerate endometrium in postmenopausal women given hormone replacement therapy.

The regenerating properties of the endometrium and its ability to support and nourish a fertilized ovum are an extremely complex system that appears to involve numerous endocrine, paracrine, and autocrine interactions. At the endometrial level, all three inhibin subunits are expressed in the human. It is believed that these dimeric glycoproteins may be involved in endometrial maturation, such as angiogenesis, decidualization, and tissue remodeling. Epidermal growth factors (EGFs) are extremely important in human embryogenesis, development, and proliferation differentiation. Human endometrial cells have been shown to express all four EGF receptors and two ligands amphiregulin and transforming growth factor alpha. Other substances with known angiogenic properties, such as leptin and erythropoietin, have also been shown to be expressed along with their receptors by human endometrium.

This process of monthly shedding and regeneration can occur as often as it does without producing permanent tissue damage possibly because most of the functional endometrium is conserved during menses and because the metamorphosis from proliferative to secretory endometria is controlled not only by processes of cell desquamation and re proliferation but also by dynamic and interactive processes of the endocrinologic and reproductive systems involving many organs. Any interruption of these normal but quite complex cyclic processes can lead to irregularities in endometrial breakdown and to AUB; the categorization of type of AUB is determined by the PALM-COEIN classification system ([Fig. 26.1](#)).

## **ENDOCRINOLOGY**

The endometrium is an endocrine organ that responds to circulating blood levels of estrogen and progesterone. These two steroids alone are sufficient to induce growth and maturation of an endometrium that can support blastocyst implantation, as has been demonstrated by their sequential administration to patients with ovarian failure to prepare for the transfer of donated embryos. Estradiol ( $E_2$ ) production by the developing follicle stimulates metabolic activity in the endometrium.  $E_2$  has multiple effects that are mediated through binding to estrogen receptors. There are two estrogen receptors: alpha and beta. The estrogen receptors are members of a hormone receptor family that includes not only the other steroid receptors but

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also receptors for vitamin D and thyroid hormone. All receptors in this family have three domains. The regulatory domain at the amino acid terminal binds regulatory protein factors. The hormone-binding domain on the carboxy terminal, with its contiguous hinge region, undergoes conformational changes when a steroid hormone binds to it, allowing DNA binding. The DNA-binding domain binds to the hormone-responsive elements in the target gene. The conformation of the DNA-binding domain consists of the highly conserved zinc finger structures that interact with complementary patterns in the DNA.

Steroid hormones have relatively low molecular weights and are rapidly transported into cells by passive diffusion. Binding of a steroid hormone to the intranuclear receptors transforms and activates the hormone receptor complex to allow DNA binding to specific hormone response elements and initiates subsequent transcription. Both estrogen and progesterone receptors bind to their response elements as dimers. After gene activation, the hormone receptor complex undergoes processing with dissociation and loss of activity.

Transcription of target genes with mRNA synthesis leads to translation with synthesis of proteins on ribosomes in the cytoplasm. The biologic effects of  $E_2$  are mediated through this protein synthesis.

### **Estrogen and Progesterone Receptor Induction**

One important function of estrogen is the induction of synthesis of its own and other steroid hormone receptors, called replenishment. Estrogen receptors reach a maximum concentration in the middle-to-late proliferative phase of the menstrual cycle. Progesterone receptors are also induced, and their concentration peaks in the late proliferative phase. Progesterone then blocks the estrogen replenishment mechanism, possibly by accelerating receptor turnover and inhibiting  $E_2$ -induced gene transcription. Enough progesterone receptors persist throughout the luteal phase, however, to maintain endometrial responsiveness and induction of decidualization.

### **Estrogen and Progesterone Target Genes**

Target genes of the  $E_2$  receptor complex code for the synthesis of numerous proteins, including structural proteins, enzymes, and growth factors. The relative roles played by the alpha and beta estrogen receptors in the endometrium have yet to be completely elucidated. The net effect of estrogenic stimulation is to induce DNA synthesis and mitotic activity with proliferation of the endometrial glands and stroma. The results are cessation of menstrual flow and an increase in the thickness of the endometrium.

Progesterone also has multiple biologic effects mediated through its receptors. It actively inhibits synthesis of both its own receptors and estrogen receptors, although sufficient progesterone receptors remain throughout the luteal phase of the cycle to mediate maturation and secretory differentiation of the endometrium. The net effect is to antagonize estrogenic metabolic activity with suppression of DNA synthesis in endometrial cells, which results in dynamic inhibition of cell mitosis. Progesterone is also responsible for the active induction of synthesis of various cytoplasmic enzymes, the secretion of proteins such as prolactin-dependent and progesterone-dependent endometrial peptide from decidualized stromal cells, and the stabilization of lysosomes, all of which may play an important role in the onset of menstruation.

### **Histology and Physiology**

The postmenstrual endometrium that remains after collapse and partial shedding during menstruation consists of a thin but stable layer of basalis cells and the dense irregular remnants of the stromal cell-derived stratum spongiosum. The glands are narrow and lined by low cuboidal epithelial cells with few mitoses. The glandular stromal cells are small and spindle shaped with little cytoplasm or mitotic activity. Protein synthesis and secretory activity are minimal. It is on this substrate of basal and stromal cells that estrogen induces a proliferative response.

### **Early Proliferative Phase**

Mitotic activity results in growth and pseudostratification of the glandular epithelial cells. With development and elongation of the glands, the epithelial cells assume a more columnar shape, with secretory granules in the cytoplasm, and glycogen begins to collect in the basal vacuoles. Arteriolar vessels grow up into the endometrium as part of the general proliferative response. The stromal cells also proliferate and expand from a dense compact state to an expanded matrix by transient edema. The combined effects of proliferation and expansion cause the endometrium to grow in this phase to a thickness of 3 to 5 mm.

The increased mitotic activity that results in proliferation is mediated by way of estrogen induction of various peptide growth factors. Epidermal growth factors and insulinlike growth factor I (IGF-I) are two potent mitogens with synthesis that is stimulated by estrogen in endometrial epithelial and stromal cells. Endothelin-1 is a vasoactive peptide with mitogenic activity; its synthesis is induced by both estrogen and growth factors, and its metabolism is enhanced by progesterone. Endothelin-1 may play a role in proliferation and in menstruation. The various peptides that are secreted from stromal and epithelial cells to form the extracellular matrix of the endometrium can be either induced or suppressed by both estrogen and progesterone. Fibronectin, for example, is suppressed by progesterone, whereas several integrin subtypes are stimulated by progesterone. These peptides may have a functional role in proliferation, differentiation, and embryo implantation.

Angiogenesis both allows repair of the endometrium after menstruation and supports cellular proliferation for regrowth during the follicular phase. It is supported and promoted by multiple growth factors. An important role is played by vascular endothelial growth factor (VEGF). Torry and Torry found VEGF mRNA expression is induced by  $E_2$  and increases from the early proliferative phase through the secretory phase. Vascular endothelial growth factor is produced by the glandular epithelial cells, although some stromal expression is evident in the secretory phase. The increased expression throughout the cycle supports a possible role of VEGF in expansion and coiling of the spiral arterials. Kooy et al. detected changes in VEGF in women with AUB, supporting a possible role in the pathogenesis of menorrhagia.

$E_2$  induces several enzymes (alkaline phosphatase,  $5\alpha$ -reductase, and possibly phospholipase  $A_2$ ).

Phospholipase  $A_2$ , which releases arachidonic acid from phospholipid esters, controls the rate-limiting step in prostaglandin synthesis.  $E_2$  also stimulates cyclooxygenase synthesis of prostaglandin  $F_{2\alpha}$  ( $PGF_{2\alpha}$ ) and prostaglandin  $E_2$  ( $PGE_2$ ), both of which have a role in menstrual function.  $PGF_{2\alpha}$  has vasoconstrictive and muscle contraction effects.  $PGE_2$  is generally a vasodilator but can also cause contractions in uterine smooth muscle. Alterations in the relative levels of  $PGF_{2\alpha}$  and  $PGE_2$  are known to change menstrual bleeding patterns.

## Late Proliferative Phase

Ovulation with corpus luteum formation and significant progesterone secretion leads to secretory transformation in the

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late proliferative phase endometrium. Progesterone inhibits both estrogen and progesterone receptor synthesis and inhibits DNA synthesis and mitosis. This inhibition process is accompanied by the development of RNA-filled channels between the nucleoli and nuclear membranes that are responsible for the progesterone-induced active synthesis of cytoplasmic enzymes during the secretory phase of the cycle.

## The Secretory Phase

The cytoplasmic enzymes  $17\beta$ - and  $20\alpha$ -hydroxysteroid dehydrogenase (HSD) are induced by progesterone and modulate steroid activity. The enzyme  $17\beta$ -HSD catalyzes the conversion of  $E_2$  to the relatively weaker estrogen estrone, which, when sulfated by estrogen sulfotransferase, can no longer bind to estrogen receptors. The enzyme  $20\alpha$ -HSD alters progesterone receptor binding and activity. Cytoplasmic lytic enzymes such as acid phosphatase are also induced by progesterone but are kept inactive within Golgi-derived lysosomes, the membranes of which are stabilized by progesterone. Insulin-like growth factor II is synthesized locally by middle-to-late secretory phase endometrium and appears to be involved in the differentiation response of the endometrium to progesterone. Insulinlike growth factor-binding protein I also appears at this time and is regulated by the IGFs and by relaxin. Other autocrine or paracrine agents secreted locally by decidual cells are relaxin, progesterone-dependent endometrial peptide, and prolactin.



Progesterone has also been shown to induce the activity of metalloendopeptidase, which degrades the endothelin-1 peptide. Withdrawal of progesterone can lead to increased endothelin-1 activity with vasospasm and initiation of menstrual bleeding. Several investigators have described increased levels of protease inhibitors, such as  $\alpha_1$ -antitrypsin and antithrombin III, in secretory phase uterine fluid, which may also be involved in the mechanism of menstrual bleeding.

## **The Luteal Phase**

Morphologically, secretory transformation of the endometrium results in coiling of the spiral arterioles and endometrial glands. The endometrium reaches its maximum thickness of 5 to 6 mm and maintains this thickness throughout the luteal phase. The subnuclear intracytoplasmic glycogen vacuoles in the basal glandular cells transpose to the apex and are expelled into the glandular lumen. The stromal cells subsequently flatten into a low cuboidal form. Stromal cell differentiation from reticular spindle-shaped cells into plump predecidual cells and phagocytic granulated cells defines two layers in the functional endometrium known as the superficial compactum and the deeper spongiosum. The spongiosum has a loose edematous matrix that is the consequence of increased capillary permeability, mediated possibly by prostaglandins. The predecidual, late secretory phase stromal cells produce several metabolically active substances, as previously described, and are infiltrated by migratory leukocytes. The release of lysosomal enzymes from endometrial cells and possibly also from leukocytes may be involved in the initiation of menstruation.

## **Menstruation**

Menstruation is controlled by many complex, interrelated, and incompletely understood factors. Normal menstruation results from progesterone withdrawal from the estrogen-primed endometrium. Changes that occur in the endometrium during menstruation were described by Markee by observation of endometrial tissue transplanted to the anterior chamber of the eyes of rhesus monkeys. Markee described cyclic changes in endometrial vascularity and the development of coiled vessels supplying the superficial two thirds of the endometrium. The estrogen-primed endometrium of the follicular phase is compact, with relatively underdeveloped vasculature. Progesterone converts this endometrium into a thick, edematous, secretory lining that is glycogen enriched and prepares the metabolically active stroma and glands with an increased vasculature to receive and nourish a fertilized ovum. If implantation does not occur, estrogen and progesterone levels fall, prostaglandin synthesis occurs, and lysosomal membranes rupture, causing constriction of the spiral arterioles, ischemic necrosis, and sloughing of the endometrium superficial to the basalis layer.

Lysosomal release and ischemic necrosis has been believed to be the main mechanism for normal menstrual bleeding for many years. However, the difficulty in detecting cell necrosis during menstruation and viability of menstrual fragments has raised a number of questions about this theory. Current data support the "metalloproteinase theory" as the mechanism leading to menstrual tissue breakdown and shedding. Matrix metalloproteinases (MMPs), lytic enzymes in conjunction with activated endometrial stromal granulocytes, macrophages, and mast cells together are now thought by most investigators to cause menstruation. It is believed that tissue inhibitors of metalloproteinases (TIMPs) remain constant throughout the menstrual cycle. Before menstruation, production and activation of MMPs increases in an environment of stable amounts of TIMPs, leading to an altered MMPs/TIMPS ratio, resulting in tissue breakdown. Estrogen and progesterone, along with cytokines, appear to play a significant role in the regulation and expressions of the MMPs. High levels of progesterone are believed to inhibit MMP production and activity. This would explain endometrial tissue breakdown that occurs coincident with decreasing progesterone levels from an involuting corpus luteum.

In the second part of the menstrual phase, mitotic activity resumes and epithelial regeneration begins. This process occurs even while menstrual bleeding continues. Horizontal growth from the stem cells of the glands present in niches within the basalis layer continues the regenerative process. New blood capillaries are formed

by the stimulating effect of VEGF and thymidine phosphorylase (TP) secreted by both epithelial and stromal cells. Continuous proliferation of stem cells is ensured by high telomerase activity.

This process begins in the premenstrual phase of the cycle with cessation of synthesis and inspissation of ground substance and supporting tissues by lytic enzymes released from lysosomes, which causes loss of fluids and compression of the endometrium, tonic contractions of spiral arterioles with reduction of blood flow to the tissues, loss of stromal edema, and kinking of the coiled spiral arterioles caused by the reduction in endometrial thickness.

A generalized state of ischemia develops in the superficial layers of endometrium, and bleeding into the stroma begins. Acid phosphatase and prostaglandin substances released from autolyzed cells, together with increased endothelin-1 activity, cause more intense vasoconstriction of spiral arterioles, and devitalized tissues finally slough as small hemorrhages in the stroma coalesce. According to Beller, coagulation factors are decreased in normal menstrual discharge. Fibrinogen is absent, plasminogen is converted to plasmin by released peptidases, and the amount of plasmin inhibitor is decreased. Menstrual blood generally does not clot, but it can form red blood cell aggregates with mucoid substances, mucoproteins, and glycogen as it collects in the vagina. These red cell aggregates may appear to be blood clots, but they contain no fibrin. In the presence of very heavy flow, however, clotting can occur.

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According to classical theory, during menstruation the superficial compacta and the intermediate stratum spongiosum layers of the endometrium are shed, leaving only the basalis layer intact. New endometrium is regenerated from the basalis. Regeneration of new capillaries from the basalis has been observed by Markee, and restoration of the endometrial circulation has been correlated with the cessation of menstrual bleeding. Blood loss from the process of normal menstruation is limited by recovery of tone in the myometrium and endometrial vasculature, cessation of cellular autolysis, eventual clotting over the endometrial surface, and eventual active regeneration of glands, stroma, and vessels in the basalis layer in response to rising estrogen levels in the new cycle. The retained basalis endometrium is protected from destruction by lysosomal enzymes by a mucinous carbohydrate coat that covers the free surfaces of endometrial cells. This mechanism for retention of some endometrium during menstruation may explain the lack of permanent damage during the years of menstruation.

Endometrial regression during menstruation is described by classical theory as the result of four processes: autophagia, heterophagia, extrusion of secretory products, and elimination of fluids with some, but not complete, shedding of tissue. Autophagia and heterophagia are the kindred processes of intracellular lytic digestion of debris in vacuoles and of extracellular lytic digestion of debris taken up by phagosomes. Both processes eliminate damaged tissue to allow regeneration of normal endometrial cells. With fluid loss and secretion, the functionalis (the remaining functional basalis) regresses to a resting state, ready to regenerate in the next cycle. These two processes can only partially explain the observation that initial endometrial regeneration occurs in the absence of estrogen. This initial lack of estrogen dependence can also be secondary to the lesser proliferative response required after regression, compared with complete endometrial shedding. Much work remains to be done to define the complex processes involved in menstruation.

## ABNORMALITIES OF THE MENSTRUAL CYCLE

### STEPS IN THE PROCEDURE

#### Evaluation of Abnormal Uterine Bleeding

- Rule out pregnancy
- Document ovulation
- Screen for medical disorders
- Endometrial biopsy if at risk for hyperplasia
- Treat underlying medical disorders
- Correct anatomic abnormalities
- Medical therapy in anovulatory women

Given the complexities and varieties of possible alterations of the systems that control menstruation, it is not surprising that AUB should occur even in the absence of obvious disease. Prolonged estrogen stimulation can result in endometrium that outgrows its blood supply and has asynchronous development of endometrial glands, stroma, and blood vessels. Any failure of progesterone production can also profoundly affect endometrial glands, stroma, and blood vessels. Abnormal synthesis of acid mucopolysaccharides can result in the release of excessive amounts of hydrolytic enzymes into the stroma. Lysosome release from endometrial glands, influenced by plasma progesterone levels, can affect menstrual flow. The endometrium and myometrium of patients with menorrhagia produce altered types of prostaglandins. Smith and associates have shown that the amount of menstrual flow is influenced by a change in the endometrial conversion of prostaglandin endoperoxide from  $\text{PGF}_2$  to  $\text{PGE}_2$  and that women with menorrhagia synthesize mainly the vasodilator  $\text{PGE}_2$  in the endometrium.

Menstruation has three clinical characteristics: the menstrual interval or cycle length, the duration of flow, and the amount of flow. The mean cycle length is 28 to 29 days, although a menstrual interval of 21 to 35 days can be considered normal. A menstrual interval shorter than 21 days and a menstrual interval longer than 35 days are considered abnormal. Amenorrhea is the absence of menses for 6 months or longer. The menstrual interval can vary from month to month by several days. Regularity of the menstrual cycle is more important than exact approximation to the 28-day mean menstrual interval. Variation in the length of the menstrual interval in regular ovulatory cycles usually occurs in the preovulatory (proliferative) phase of the cycle and is more frequent among postmenarchal teenagers and in women approaching menopause.

A duration of flow of 7 days or less is considered normal. A patient bleeding beyond 7 days enters the intermenstrual phase of the cycle, which was previously defined as metrorrhagia and is now categorized by the American Congress of Obstetricians and Gynecologists (ACOG) as intermenstrual AUB. Regardless of the length of the menstrual flow, 70% of the blood loss usually occurs by the 2nd day and 90% by the 3rd day. The mean menstrual blood loss for a normal period is approximately 40 mL. A total blood loss of 20 to 80 mL, representing 10- to 35-mg iron, has long been accepted as within the normal range. Menstrual blood loss of 80 mL or less was established as the upper limit of normal, as this is the 95th percentile in healthy women with normal iron stores measured in a population of Swedish women in the 1960s. The clinical utility of these measures is very limited. Additionally, it has recently been shown that the 80-mL value has neither the sensitivity nor specificity for disease, compromised iron status, or adverse impact of periods. The determination of the normalcy of menstrual bleeding amount is better addressed in a clinical context. Concerns about anemia in a particular patient should be investigated with appropriate laboratory tests for iron stores. A thorough menstrual history should establish the patient's perception of the heaviness of her flow, impact on her life, difficulty with containment of flow, and associated symptoms. Quantitation of menses is difficult, and a perfect measurement tool does not exist. There have been multiple survey questionnaires that have attempted to objectively measure menstrual bleeding. These measures include surveys such as the validated Menorrhagia Impact Questionnaire (MIQ) and menstrual calendars described by Bushnell and colleagues. Although the Uterine Fibroid Quality of Life questionnaire developed and validated by Spies et al. is designed for fibroid patients, there are a number of questions within the survey that assess bleeding.



We believe that development and routine use of a convenient, standardized, objective method for measuring menstrual blood loss would significantly improve the clinical practice of gynecology. Iron deficiency anemia is a late manifestation of excessive menstruation. Serum iron (ferritin) levels are more sensitive than hematocrit and hemoglobin levels for detection of iron depletion before anemia develops, as shown by Guillebaud and colleagues. The method of Hallberg and Nilsson for quantification of iron and blood loss is based on

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the simultaneous use of tampons and pads for the collection of menstrual blood. Menstrual blood is extracted with 5% sodium hydroxide, which converts hemoglobin to alkaline hematin. The concentration is then determined spectrophotometrically. The method is simple and gives accurate results but is not widely used outside of clinical investigations.

## Acute Abnormal Uterine Bleeding

### STEPS IN THE PROCEDURE

#### Acute Abnormal Uterine Bleeding

- Determine patient acuity (hemodynamically unstable or hypovolemic patients require immediate intravenous access)
- Determine etiology using the PALM-COEIN classification system
- Select appropriate medical or surgical treatment

Patients who have an episode of bleeding that is sufficient to require immediate intervention should be approached in three stages. First, the patient should be rapidly assessed to determine acuity. Patients who are hemodynamically unstable should have one or two large-bore intravenous lines started in the event transfusion, or clotting factor replacements are necessary. Second, the etiology of the bleeding should be determined. The determination of etiology should be guided by the PALM-COEIN classification system, which separates causes into the two broad categories of “related to structural abnormalities” and “unrelated to structural abnormalities” (Fig. 26.1). Finally, an appropriate treatment should be chosen.

Similar to nonacute abnormal bleeding, described in the following sections, the treatment of acute bleeding is medical or surgical. Hormonal management using intravenous (IV) conjugated equine estrogens can stop bleeding within 8 hours in 72% of patients compared to placebo. Oral contraceptives or progestins can be used to manage bleeding chronically. Mechanical and surgical methods to manage acute bleeding include the use of intrauterine tamponade with a 26-F Foley catheter inflated with 30 mL of saline, dilatation and curettage, and in rare cases hysterectomy. Case reports have shown that both uterine artery embolization and endometrial ablation can successfully control acute AUB according to the American Congress of Obstetricians and Gynecologists Committee Opinion on the management of acute AUB.

## Abnormal Uterine Bleeding Ovulatory Dysfunction

The state of chronic anovulation is the result of unopposed estrogen stimulation of the endometrium with consequent irregular breakdown and bleeding. Chronic anovulation syndrome is a “wastebasket” diagnosis for multiple endocrine etiologies. Hyperthyroidism and hypothyroidism, hyperprolactinemia, hormone-producing ovarian tumors, and Cushing disease are all endocrine syndromes that can induce anovulation, but the primary etiology of abnormal uterine bleeding ovulatory dysfunction (AUB-O) is chronic anovulation syndrome, often commonly described as the polycystic ovary or Stein-Leventhal syndrome. Any imbalance in hypothalamic

pulsatile release of gonadotropin-releasing hormone (GnRH), in pituitary synthesis or release of follicle-stimulating hormone (FSH) or luteinizing hormone (LH), or in ovarian follicular production of E<sub>2</sub>, androgens, or progesterone can upset the delicate balances that induce cyclic ovulation and normal menstrual function. Exogenous androgen production in the adrenal glands and estrone production in adipose tissue produce identical clinical pictures.

Anovulation is also more common at the extremes of reproductive life. Perimenarchal and perimenopausal women require evaluations modified to include diagnoses that are less common in the mid reproductive years, such as coagulopathies in the perimenarchal patient and endometrial hyperplasia in the perimenopausal patient.

Menorrhagia has been described as an early symptom in patients with subclinical hypothyroidism before diagnosis of overt disease. Thyroid replacement in a normal physiologic dosage should resolve the abnormal bleeding. Because this is one of the less common causes of AUB, there is some controversy about whether thyroid testing should be part of the initial screening of patients with AUB.

Although anovulation is a frequent cause of AUB, histologic studies consistently show that 15% to 20% of AUB patients have secretory endometrium, indicative of at least intermittent, if not regular, ovulation. Livingstone and Fraser provide evidence to suggest that ovulatory AUB is more common than AUB that is associated with ovulatory dysfunction. The differential diagnosis of abnormal bleeding with ovulation differs from that of anovulation. Ovulatory patients with abnormal bleeding are more likely to have an underlying organic pathology and are not; therefore, true AUB-O patients by strict definition.

Aksel and Jones studied endometria of patients with AUB and found hyperplasia in 63% of cases; secretory endometrium was observed in 17%, and no secretory endometrium of the interval, postmenstrual, or atrophic type made up the remaining 20%. Thus, at least 17% of patients in this series had normal cyclic hormonal function and ovulation before the endometrium was examined, and it is possible that many patients with the postmenstrual type of endometria would have shown secretory changes if curettage had been performed somewhat later. In addition to histologic confirmation of ovulation by the presence of secretory endometrium, ovulation can be documented by basal body temperature charting, urinary LH surge detection, or prospective hormonal evaluation. In some cases, the prospective hormonal studies using daily serum estrogen and progesterone levels are more accurate for defining ovulatory status than are the historically accepted studies of endometrial histology, which can be misleading because of previous hormonal therapy. Although serum progesterone concentration exceeding 3 ng/mL in the luteal phase of the cycle indicates ovulation, a single measure will only identify the presence of ovulation in that cycle. Serial measures may be necessary to identify the patient that is anovulatory on an intermittent basis.

### **Abnormal Uterine Bleeding Coagulopathy**

Proper evaluation of abnormal bleeding in the ovulatory patient demands assessment for other less common causes of bleeding. According to Claessens and Cowell, bleeding dyscrasias are particularly common in perimenarchal patients, up to 19% of whom have a primary coagulation disorder, such as idiopathic thrombocytopenic purpura or von Willebrand disease. An ad hoc consensus conference that met in May 2004 concluded that underlying hemostatic disorders were a more common cause of menorrhagia in adult women than has been currently recognized. The most common of

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these coagulopathies is von Willebrand disease. The incidence of von Willebrand disease in the general population has been estimated at 0.8% to 1.3%. The consensus conference calculated, by review of the literature, an incidence of 13.2% (range 11.2% to 15.5%) in healthy women with menorrhagia. Conversely, women with von Willebrand disease report menorrhagia in 78% to 93% of patients. If von Willebrand disease is excluded, the inherited disorders of hemostasis are relatively rare. Disorders of platelet number and function

have variable effects on menstrual bleeding, depending on their severity. Treatment of AUB secondary to coagulopathy may involve medical management with tranexamic acid, desmopressin acetate (DDAVP), hormonal therapy, or a progestin-containing intrauterine device (IUD). Endometrial ablation is also appropriate in these patients.

### **Abnormal Uterine Bleeding Iatrogenic**

Hemorrhagic diatheses can occur with leukemia, with chemotherapy treatment, or secondary to oral anticoagulant therapy or ingestion of foods or drugs that inhibit platelet aggregation. Women taking anticoagulants are at risk for iatrogenic AUB. Hormonal interventions such as oral contraceptives can also result in abnormal bleeding patterns rather than improvement of symptoms. The lowest doses of oral contraceptives are more likely to be associated with spotting than formulations containing 35 µg of ethinyl estradiol. Kaunitz et al. report a higher likelihood of unscheduled bleeding with continuous and extended-cycle regimens such as Seasonale, Seasonique, and Lybrel than with the traditional 28-day schedule.

### **Abnormal Uterine Bleeding Not yet Classified**

Although infection is considered to be a cause of AUB, infection is not one of the categories identified under the PALMCOEIN classification system. This category would therefore be classified as not yet classified. Mobiluncus species identified in cases of abnormal bleeding respond to oral metronidazole therapy. Chlamydia has been implicated in abnormal bleeding, particularly with concurrent use of oral contraceptives.

Arteriovenous malformation is a very rare cause of ovulatory bleeding. In a report by Fleming and colleagues, only two cases were diagnosed before definitive surgery; the diagnosis was by pelvic angiography.

The reported association between tubal ligation and new onset of AUB should also be noted. Although numerous anecdotal reports exist, no underlying pathologic changes in anatomy or hormone production have ever been documented. Long-term follow-up studies do not confirm an increased incidence of abnormal bleeding in these patients, but do implicate biased patient perception. Patients who discontinue oral contraceptive use after tubal ligation have heavier and more painful bleeding, whereas patients who have intrauterine devices removed after sterilization have improved menstrual symptomatology.

## **Pathophysiology**

As stated earlier, the most common etiology for AUB is estrogen withdrawal or estrogen breakthrough bleeding in an anovulatory patient. In the absence of progesterone exposure to cause inhibition of DNA synthesis and mitosis, the estrogenic proliferative response causes stromal cell growth to exceed the structural integrity of its stromal matrix, and the endometrium breaks down with irregular bleeding.

Unopposed estrogen results in vascular endometrial tissue with relatively scant stroma, giving glands a back-to-back appearance. The endometrium is fragile and undergoes repetitive spontaneous breakdown. In the absence of normal control mechanisms to limit menstrual blood loss, bleeding can be prolonged and excessive.

Other contributing factors are the lack of coordinated vasoconstriction and the release of lytic enzymes, which occurs in a normal progesterone-stimulated endometrium. The absence of progesterone stimulation of metalloendopeptidase increases endothelin-1 activity, which contributes to vasospasm. Lysosomal enzymes inappropriately released in the absence of progesterone stabilization of the lysosomal membrane further contribute to structural breakdown. The same lytic enzymes, MMPs, and their inhibitors involved in normal menstrual bleeding have been found to have aberrant locally restricted expression, activation, and uncontrolled activity in the endometrial tissue biopsy specimens from women with metrorrhagia.

Many questions still remain about the mechanisms responsible for all cases of AUB. Although the

mechanisms described above can explain some cases of AUB, it does not explain clinical scenarios such as bleeding unresponsive to hormonal manipulation after structural lesions have been ruled out. Hemostasis in a bleeding endometrium depends both on coagulation, with thrombus formation forming plugs in superficial blood vessels, and on vasoconstriction of spiral arterioles; generalized endometrial collapse with compression of bleeding vessels can also contribute. The lack of coordinated vasoconstriction and the irregular structural collapse lead to irregular and often heavy bleeding. The amount of bleeding correlates directly with the level of estrogen stimulation. The chronic high estrogen milieu seen in cases of obesity and chronic anovulation, and in perimenarchal and perimenopausal patients, cause the greatest amount of AUB blood loss.

Unopposed estrogen stimulation can, over time, induce a hyperplastic response in the proliferating endometrium (Fig. 26.2). Such hyperplasia can eventually develop the cytologic changes associated with neoplasia: atypical adenomatous hyperplasia or even low-grade adenocarcinoma. Such cellular transformation takes time, as much as 10 to 20 years; a young patient with AUB has a low risk of hyperplasia or neoplasia and generally does not require endometrial sampling. Patients with a long history of chronic anovulation are at greater risk of hyperplasia and undergo histologic evaluation earlier. The perimenopausal patient has a substantially higher risk, however, and sampling is mandated.

**Diagnostic Imaging Techniques**

Diagnostic vaginal ultrasound can be particularly useful in cases of ovulatory AUB. A nonrandomized study of 45 otherwise unselected patients with AUB demonstrated anatomic pathology in 31% by vaginal ultrasound compared with 9% by clinical examination. Pathologic findings included leiomyoma uteri, polyps, and abnormal endometrial architecture. If these data are confirmed by later studies, the implication is that true AUB in ovulatory patients may be even more rare than the currently accepted figure of 15% to 20%. Endovaginal ultrasound is also of particular value in cases of perimenopausal and postmenopausal abnormal bleeding, which will be discussed later (Fig. 26.3).

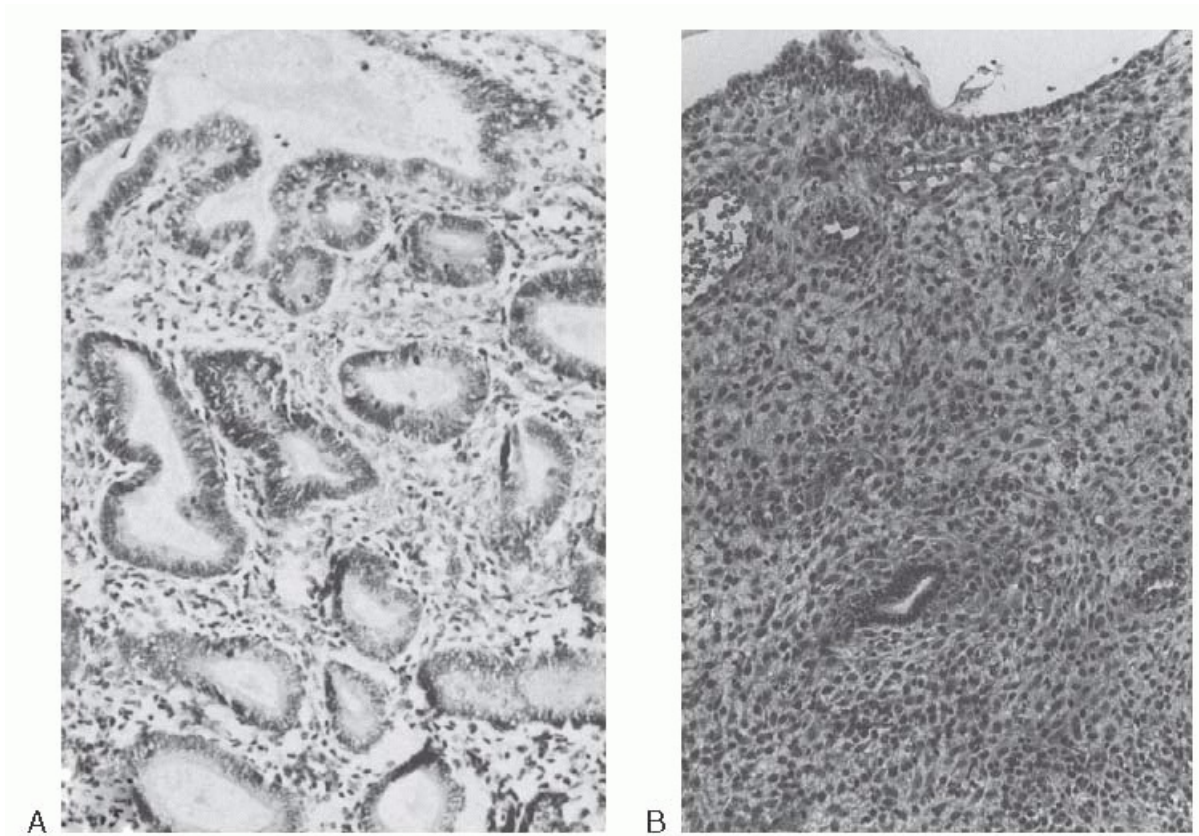
Saline infusion sonography (SIS) is a technique to improve visualization of the endometrial cavity during transvaginal ultrasonography. Dueholm and colleagues compared the accuracy of SIS with transvaginal sonography, hysteroscopy, and magnetic resonance imaging (MRI). In 108 patients with AUB, pain, endometriosis, or myomas, SIS had an overall sensitivity comparable to the gold standard of hysteroscopy and better than either MRI or transvaginal sonography. Magnetic resonance imaging had the highest sensitivity for submucous

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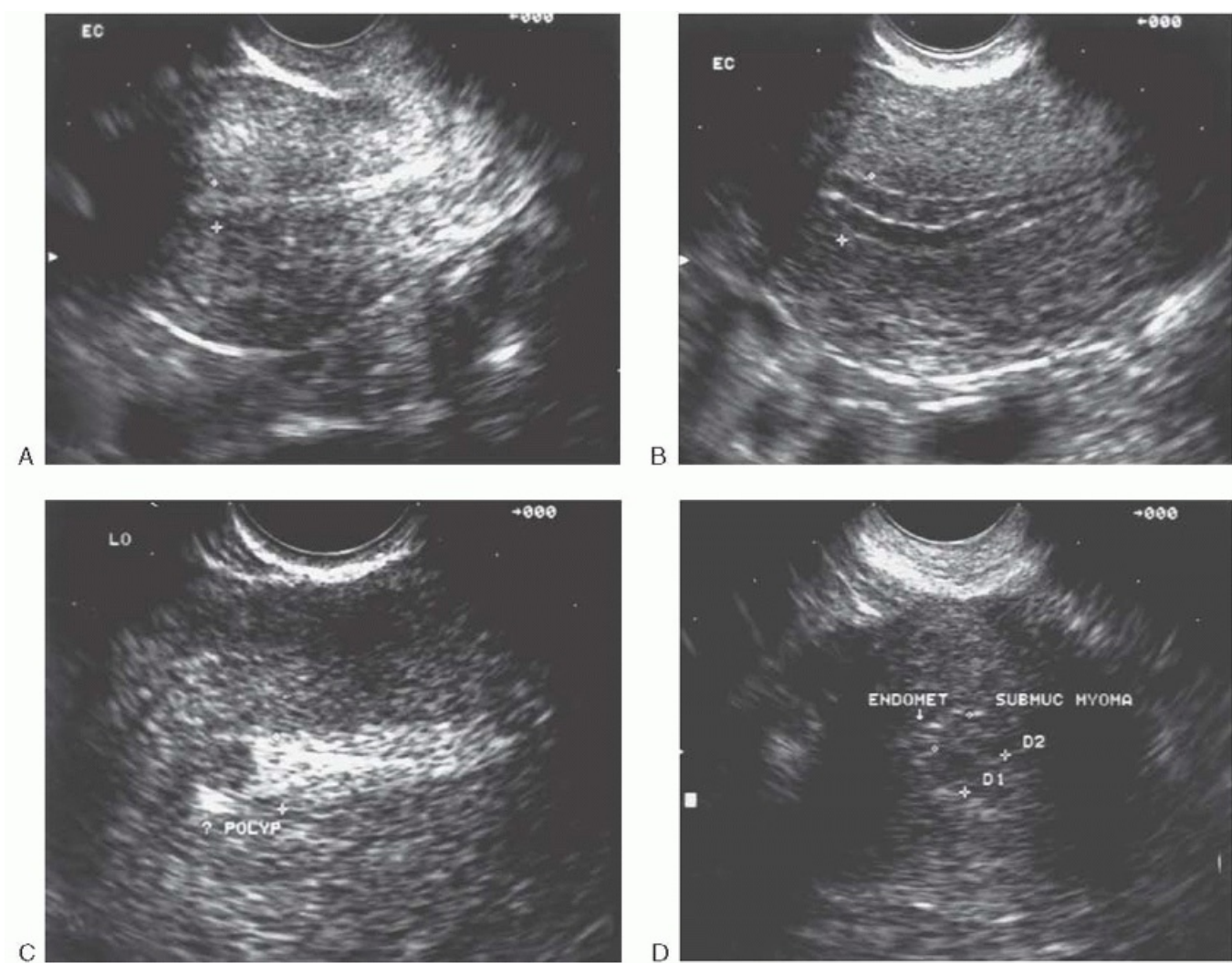
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myomas, but a relatively low sensitivity for other intrauterine pathology, such as polyps. As SIS is a less invasive procedure than a surgical technique, such as hysteroscopy, and is much less expensive than MRI, it should be the procedure of choice for imaging of the endometrial cavity in patients with AUB.





**FIGURE 26.2 A:** Endometrial hyperplasia before treatment showing hyperplastic cellular changes of glands. **B:** Hyperplastic endometrium after continuous progestin treatment.





**FIGURE 26.3 A:** Single-line endometrium consistent with postmenstruation, early proliferation, and postmenopause. **B:** Three-line endometrium from estrogen stimulation, late follicular phase. **C:** Endometrial polyp in hyperechoic thickened endometrium consistent with luteal phase or hyperplasia-neoplasia. **D:** Submucous myoma with distortion of endometrial cavity marked by single-line endometrium.

## Differential Diagnosis of Abnormal Uterine Bleeding

Abnormal uterine bleeding occurs most frequently at the extremes of menstrual life, but it can develop at any intervening time. The characteristics of AUB are variable, from infrequent heavy flow (oligomenorrhea) to almost continuous spotting or bleeding. The age at onset and duration of irregularity can provide important clues to etiology. Anovulation is common in the perimenarchal girl. More than 50% of cycles are anovulatory in the first 2 years after menarche. Complications of pregnancy also are common in this age group and must be ruled out before initiation of treatment for AUB. New sensitive radioimmunoassays for the beta subunit of human chorionic gonadotropin are accurate for evaluating the possibility of pregnancy. Although relatively rare, endocrinologically active ovarian neoplasms do occur and should be particularly excluded in prepubertal vaginal bleeding. Other causes of irregular bleeding in the adolescent include genital trauma and coagulopathies such as idiopathic thrombocytopenic purpura and von Willebrand disease. As previously mentioned, the Claessens and Cowell review of children's hospital admissions for menorrhagia reports an overall 19% incidence of primary coagulation disorders and a 50% incidence in patients presenting at the time of menarche. Some more recent studies have disputed this high figure and cited a lower risk of 5%. Given the new data on von Willebrand disease in adult female menorrhagia, this newer figure is questionable, and coagulopathies should still be considered a significant cause of AUB in adolescents. The most common diagnosis is idiopathic thrombocytopenic purpura, but platelet disorders such as von Willebrand and Glanzmann diseases, thalassemia, and leukemia are also found.

The adult patient with AUB can have either an acute or a chronic history of menstrual irregularity. Onset at menarche and persistence into adulthood is a classic history for chronic anovulation syndrome, but nonclassical adrenal hyperplasia must be differentiated when there is coexistent androgen excess. The differential diagnosis can be made by obtaining a baseline 17 $\alpha$ -hydroxyprogesterone level. A level less than 200 ng/dL rules out partial adrenal 21-hydroxylase enzyme deficiency. An elevated baseline 17 $\alpha$ -hydroxyprogesterone requires a cosyntropin stimulation test to confirm the nonclassical adrenal hyperplasia diagnosis. A more acute history requires a differential diagnosis of other endocrinologic causes of anovulation, for example, thyroid and prolactin disorders, complications of pregnancy, neoplastic processes such as fibroids or hormoneproducing ovarian tumors, intrauterine lesions such as polyps and synechiae, and coagulopathies. Adult patients with menorrhagia are at higher risk than previously thought to have a bleeding diathesis. Dilley and colleagues identified coagulopathies in 10.7% of 121 patients in a case-control study. The majority of cases were von Willebrand disease. Women older than the age of 30 years with a history consistent with chronic anovulation should undergo endometrial sampling because of their greater risk of hyperplasia and neoplasia. Perimenopausal women with AUB have an even higher risk of hyperplasia and neoplasia and should always undergo endometrial sampling. Several years before menopause, menstrual cycles usually shorten secondary to a decreased proliferative phase, with resultant moderate elevation of FSH and subsequent frequent anovulatory cycles. This unopposed estrogen environment is conducive to the development of both AUB and hyperplasia. Appropriate evaluation of the premenopausal and postmenopausal patient will be discussed later in this chapter.

A diagnosis of AUB is often a diagnosis of exclusion. Problems of pregnancy such as incomplete or missed abortion, subinvolution of the placental site, placental polyp, trophoblastic disease, and extrauterine pregnancy must be ruled out. All gynecologic malignancies can cause abnormal bleeding. Common epithelial tumors of the ovary can produce estrogen and cause uterine bleeding. Submucous leiomyoma and endometrial polyps can be

present in older women but are not a problem in the differential diagnosis of adolescents. Excessive anovulatory bleeding is common with polycystic ovarian disease, with functional cysts of the ovary. The patient workup for AUB should include a complete history and physical examination. Pelvic examination may disclose an adnexal mass, evidence of genital trauma or laceration, or a fibroid uterus. Laboratory studies should include thyroid function tests and the evaluation of levels of human chorionic gonadotropin, FSH, LH, prolactin, and serum androgens, if indicated. A significant increase in dehydroepiandrosterone sulfate indicates a need to screen for nonclassical adrenal hyperplasia. A serum progesterone level measurement is useful for assessment of ovulatory status. A complete blood count with platelet and coagulation studies is appropriate, and in some cases, a bleeding time may be indicated to assess platelet function. As mentioned earlier, endovaginal ultrasound and SIS are valuable adjuncts to pelvic examination. They are particularly informative for assessment of intrauterine or extrauterine pregnancies and pelvic masses detected on examination. Occasionally, they also may reveal anatomic pathology not detected by other means (**Fig. 26.3**). Invasive tissue-sampling procedures include endometrial sampling and sampling at the time of hysteroscopy. Diagnostic hysteroscopy can be an office procedure and has replaced blind D&C as a diagnostic test. Diagnostic hysteroscopy, with its lower false-negative rate, is preferable in the perimenopausal or postmenopausal patient. An office endometrial biopsy or diagnostic hysteroscopy is not necessary in adolescents, as patients of this age are unlikely to have structural lesions such as fibroids and polyps or endometrial hyperplasia. Hysterosalpingography and hysteroscopy will be reviewed later in this chapter.

## Treatment

Because most patients with AUB have an underlying etiology of chronic anovulation with unopposed estrogen stimulation of the endometrium, medical treatment with progestational compounds is the mainstay of therapy. Precise amounts can differ depending on the patient's age, but adequate progestin stimulation will decrease DNA synthesis and cell proliferation, deplete estrogen receptors, and increase the conversion of  $E_2$  to the less potent estrone sulfate. These effects will induce maturation of the endometrium, healing of superficial breaks, and enhancement of the stromal matrix with increased structural stability and cessation of bleeding. Withdrawal of the progestin after adequate exposure results in orderly and uniform shedding of the endometrium with a finite self-limited bleed. The progestin dosage and duration of therapy must induce a complete secretory transformation; otherwise, complete inhibition of all estrogenic effects will fail, and islands of proliferative endometrium will remain.

Although postmenopausal estrogen replacement doses are low, progesterone is needed to prevent hyperplasia. Whitehead and Frazier have shown that postmenopausal estrogen

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replacement mimics the unopposed estrogen environment of chronic anovulation and that 4% of patients develop endometrial hyperplasia with only 7 days of progestin exposure, 2% with 10 days of exposure, and 0% with 12 days of exposure. They recommend 12 days of progestin every month to counteract the estrogen proliferative effects. Medroxyprogesterone acetate 10 mg, or norethindrone acetate 5 mg per day, may be prescribed. After initial control of the dysfunctional bleeding, the 12-day course can be repeated at monthly intervals to prevent the development of hyperplasia. It is convenient to start each new course on the 1st day of each month. A regular withdrawal can be expected to start either during the last 2 days of progestin or within several days of the last dose. Failure to withdraw could signify pregnancy, development of a hypoestrogenic state, or, rarely, induction of ovulation by progestin stimulation of the estrogen-primed patient. In such a case of endogenous progesterone production, the menses can be delayed 2 weeks. A word of caution: This regimen is not contraceptive. It should also be noted that the numbers of women using hormonal therapy (HT) have markedly decreased since the Women's Health Initiative (WHI). In one study by MacLennan and colleagues, 64% of women using HT prior to the WHI study discontinued treatment.

An alternative method for delivery of a progestin to control dysfunctional bleeding and menorrhagia is local administration with a progestin-impregnated IUD. Numerous studies have demonstrated significant reductions in menstrual blood loss in patients using the progestin-impregnated IUD. Xiao and colleagues showed reductions of more than 80% at up to 36 months. Irvine and associates performed a randomized trial of 44 women with menorrhagia, comparing a levonorgestrel IUD with cyclic progestin therapy. The IUD group had blood loss reduced by 90%, along with higher patient satisfaction, compliance, and continuation. In a comparison of endometrial resection with the levonorgestrel IUD, Rauramo et al. showed highly significant decreases in menstrual blood loss with both treatment arms. The incidence of complications was similar in both groups, and 3-year follow-up rates were similar. Seventeen percent of the resection group required follow-up surgery. Other studies have shown a significant cost benefit to the use of the levonorgestrel IUD compared with surgical management of AUB, including hysterectomy. As noted earlier, the levonorgestrel IUD has also shown to be effective in controlling menorrhagia in patients with hemostatic disorders such as von Willebrand disease.

New research from the Los Angeles Biomedical Research Institute (LA BioMed) found a progestogen-only treatment halted bleeding in women suffering from severe menorrhagia. In a group of 48 women, Ammerman and Nelson found that injection of depo-medroxyprogesterone acetate 150 mg intramuscularly combined with 3 days of oral medroxyprogesterone acetate 20 mg every 8 hours for 9 doses had a mean time to bleeding cessation of 2.6 days, with high patient satisfaction.

Chronic unopposed estrogen can produce a very lush endometrium that can bleed heavily during progestin withdrawal. Speroff and colleagues recommend treatment using combination oral contraceptives in a step-down regimen. Two to four pills are given daily, one every 6 to 12 hours, for 5 to 7 days for acute control of bleeding. This will usually control acute bleeding within 24 to 48 hours, allowing time to complete the diagnostic evaluation. Withdrawal of medication will result in a heavy bleed. On the 5th day of this bleed, a low-dose cyclic oral contraceptive is started and repeated for three cycles to allow orderly regression of the excessive proliferative endometrium. Alternatively, the dosage of combination pills can be tapered (four times a day, then three times a day, then two times a day) over 3 to 6 days and then continued at one pill every day. Combination oral contraceptives induce atrophy of the endometrium because the chronic estrogen-progestin exposure suppresses pituitary gonadotropins and inhibits endogenous steroidogenesis. They are useful for long-term management of AUB in patients without contraindications and have the added benefit of pregnancy prevention. Particularly in perimenarchal patients, heavy prolonged bleeding can denude the basal endometrium and make it unresponsive to progestins. Curettage for control of hemorrhage is contraindicated because of a high risk of development of intrauterine synechiae (Asherman syndrome) if the basalis is curetted. High-dose intravenous estrogen (conjugated estrogens 25 mg every 4 hours until bleeding abates) will give acute control by proliferative repair of the endometrium and by direct effects on coagulation, including increased fibrinogen and platelet aggregation. Megestrol 20 mg twice daily is also an excellent method for obtaining acute control of AUB without the side effects of intravenous estrogen treatment. It will be effective in any situation other than one in which the entire endometrium has sloughed, leaving only basalis. A progestin alone or oral conjugated estrogens in combination with a progestin can then be used to induce orderly withdrawal bleeding.

Although tranexamic acid has been available for a number of years, it has come into more widespread use. In a doubleblind placebo-controlled study by Lukes et al., women who received tranexamic acid ( $n = 115$ ) had significantly greater reduction in menstrual blood loss of -69.6 mL (40.4%) compared with -12.6 mL (8.2%) in the 72 women who received placebo ( $P < 0.001$ ). They also had a reduction of menstrual blood loss that exceeded the prespecified amount of 50 mL. Finally, they had a reduction of menstrual blood loss that was considered meaningful to women. Compared with women receiving placebo, women treated with tranexamic acid experienced significant improvements in limitations in social or leisure and physical

activities, work inside and outside the home, and self-perceived menstrual blood loss ( $P < 0.01$ ).

Selective progesterone receptor modulators, such as ulipristal acetate (UPA), have been shown by Nieman et al. to be efficacious in the treatment of leiomyoma, and have been noted to cause amenorrhea in the vast majority of patients. Treated patients developed anovulatory amenorrhea without becoming hypoestrogenic, suggesting that decreased bleeding is mediated by a direct endometrial effect as well as inhibition of ovulation. Ulipristal acetate is currently only available as emergency contraception in the United States and for the treatment of leiomyoma in Europe, but may have potential use as a treatment of AUB.

Hysteroscopy of patients who fail to respond to hormonal therapy may reveal previously missed pathology, such as a submucous myoma or polyp. These diagnoses are particularly common in patients with ovulatory dysfunctional bleeding. If a diagnostic curettage has not been previously performed, one can be performed in conjunction with the hysteroscopy, both for diagnosis and for temporary therapy. The ACOG no longer considers D&C long-term therapy. If atypical hyperplasia has been identified and preservation of fertility is desired, more aggressive progestin therapy is recommended. Medroxyprogesterone acetate, 30 mg, or megestrol 20 to 40 mg daily for 3 months, should be prescribed, and the patient should be monitored by repeat endometrial sampling to assess the efficiency of the medical treatment ([Fig. 26.2B](#)). If atypical hyperplasia persists, very high-dose progestin protocols can be tried, but hysterectomy must be considered. Menorrhagia can be reduced when  $PGE_2$  and prostacyclin synthesis are decreased by nonsteroidal anti-inflammatory

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medications. These drugs inhibit the cyclooxygenase enzyme necessary for endometrial production of prostaglandin under estrogen stimulation and thus alter the relative production of the proaggregation vasoconstrictor thromboxane  $A_2$  and the antiaggregation vasodilator prostacyclin. Pathology studies have confirmed that this improves both platelet aggregation and vasoconstriction. Fraser and colleagues demonstrated these compounds to be most effective when given in therapeutic dosages for 7 to 10 days before the expected onset of the next menstrual period in ovulatory AUB patients, but they are commonly started with the onset of menses and continued throughout the bleeding episode with good success.

For coagulation disorders, 1-desamino-8-D-arginine vasopressin (also known as desmopressin or simply DDAVP) increases coagulation factor VIII with a therapeutic effect lasting approximately 6 hours. It is best administered intravenously, 0.3  $\mu$ g/kg in 50 mL saline over 15 to 30 minutes, but can be used intranasally. Antifibrinolytic agents such as  $\epsilon$ -aminocaproic acid and tranexamic acid can decrease blood loss up to 50%, but their significant central nervous system and gastrointestinal side effects and the purported risk of intracranial arterial thrombosis have traditionally limited their applicability. New data do not support a significant thrombotic risk, and tranexamic acid is widely available in Europe for use in menorrhagia. Ergot derivatives are ineffective for treatment of menorrhagia. Local delivery of progestational agents by way of an intrauterine device has been demonstrated by Milsom and colleagues to be extremely effective, with more than a 90% reduction in bleeding in some patients. This has the potential to provide long-term therapy for patients with chronic bleeding unresponsive to other therapies.

Long-acting derivatives of GnRH agonists down-regulate pituitary synthesis of FSH and LH and induce a "medical menopause." Withdrawal of endogenous steroid stimulation will result in endometrial atrophy. Various delivery options are available, including intranasal delivery, daily subcutaneous delivery, monthly intramuscular depot, and subcutaneously implanted pellet analogue. Gonadotropin-releasing hormone agonists are not effective in acute control of abnormal bleeding. At least 2 to 4 weeks are required for adequate suppression of gonadotropin production and inhibition of steroidogenesis. Long-term therapy can effectively control blood loss with chronic AUB secondary to chronic systemic illness, thrombocytopenia, or other coagulopathies. Because of the profoundly hypoestrogenic state induced by these drugs, there is



accelerated bone resorption and the risk of development of significant osteoporosis. Therefore, long-term therapy requires “add-back” treatment with an estrogen-progestin combination to prevent bone loss. Gonadotropin-releasing hormone agonists can also be used as adjuncts for endometrial preparation before endometrial ablation.

Ablation or destruction of the endometrium has been advocated for treatment of chronic abnormal bleeding unresponsive to medical management in the presence of a normal endometrial cavity and the absence of submucous leiomyomata, endometrial hyperplasia, or neoplasia. Although there has been significant disagreement regarding the appropriate indications for this procedure, it has been widely applied with varying success. The original methods included use of hysteroscopy with electrosurgical roller-ball cauterization or endomyometrial resection using a loop electrode. These hysteroscopic surgical techniques require special training. More recently, new techniques have been described to ablate the endometrial cavity without the requirement for hysteroscopy. These include thermal balloon ablation, direct instillation of heated saline, cryoablation with a cryoprobe, microwave endometrial ablation, and use of radiofrequency electromagnetic energy. Success rates reported with the various techniques have ranged from 60% to 95% of patients achieving either hypomenorrhea or amenorrhea. Brooks and Donnez et al. report pretreatment with danazol, GnRH analogues, or suction curettage to thin the endometrium appears to improve long-term success rates. Seeras and Gilliland reported resumption of menstruation in 44% of women after ablation if they had not received preoperative endometrial suppression.

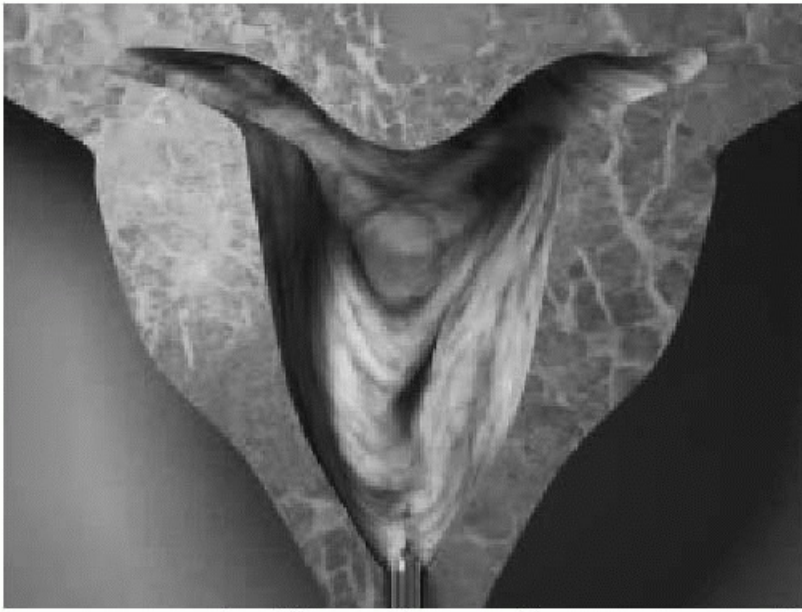
A number of comparison studies have looked at success rates of the various techniques to determine relative efficacy, complication rates, and relative cost. Meyer and colleagues compared roller-ball ablation with thermal balloon ablation in a prospective, randomized trial. A greater percentage of women in the roller-ball group (27.2%) were amenorrheic at their 12-month follow-up than were women in the uterine balloon group (15.2%). The rates of hypomenorrhea plus amenorrhea were not significantly different (balloon, 80.2%; roller ball, 84.3%). Overall patient satisfaction was equivalent. The complication rate was 3.2% in the hysteroscopic roller-ball group with no significant intraoperative complications in the thermal balloon group. A comparison of thermal balloon ablation with the progestin-containing IUD showed similar results as far as overall satisfaction; however, bleeding scores were lower and amenorrhea rates higher in the IUD group (Busfield et al.). Corson, with follow-up by Goldrath, performed a prospective randomized trial of endometrial ablation using the Hydro ThermAblator (HTA; Boston Scientific Corporation, Natick, MA, USA) versus roller ball (**Figs. 26.2** and **26.4**). This system uses heated saline flowing free under low pressure to ablate the endometrium under hysteroscopic guidance. Success rates for both groups were comparable at 3 years with amenorrhea rates of 53% for HTA and 46% for roller ball and overall satisfaction rates of 98% and 97%, respectively. There were no significant differences in complication rates or repeat surgical procedures.

The NovaSure system (Cytac Corporation, Palo Alto, CA, USA) uses radiofrequency current through a mesh electrode that conforms to the endometrial cavity to ablate the endometrium. Tissue desiccation is rapid compared with thermal devices and requires no pretreatment of the endometrium. The overall success rate of 88.3% and amenorrhea rate of 41% for NovaSure-treated patients were higher than 81.7% and 35% rates, respectively, for endometrial resection in a randomized

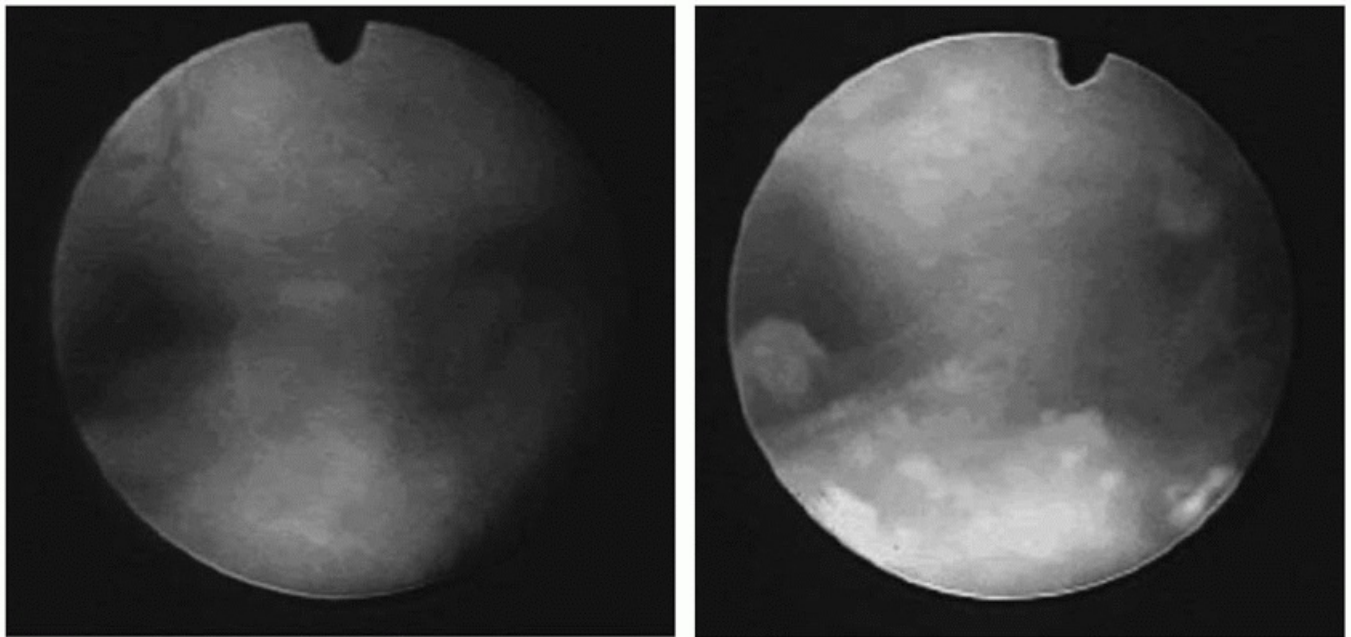
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trial by Cooper et al. A randomized trial versus hydrothermablation (**Fig. 26.5**) also demonstrated higher amenorrhea rates. Microwave energy can also be used to ablate endometrium. The MEA (Microsulis Americas, Pampano Beach, FL, USA) device was tested in a prospective randomized trial by Cooper et al., comparing it with roller-ball ablation. Success rates were 87% and 83.2%, respectively, for MEA and roller ball. Amenorrhea rates were 61.3% for MEA and 51% for the roller-ball group. This trial also included patients with up to 3-cm submucous myomas. Subgroup analysis did not show any difference in the

success rate in this group.



**FIGURE 26.4** Hydro ThermAblator. (HTA; Boston Scientific Corporation, Natick, MA, USA.)



**FIGURE 26.5** Endometrial cavity before and after endometrial ablation using Hydro ThermAblator.

Endomyometrial resection has been reported by Kooy et al. to have higher amenorrhea rates compared with rates for other techniques. Vercellini and colleagues compared myometrial resection with endometrial ablation using a vaporizing electrode similar to a roller ball. Amenorrhea rates were 48% for the endomyometrial resection group and 36% for the ablation group, although overall patient satisfaction rates were equivalent. Difficulty of surgery and mean fluid deficit were both described as greater in the resection group. In a comparison of endometrial ablation with laser versus endomyometrial resection, Battacharya et al. showed equivalent amenorrhea rates of approximately 45%, with overall patient satisfaction rates of 90%.

Operative hysteroscopic techniques require specialized training, and complications, although relatively infrequent, can be significant. A multihospital survey by Jansen et al. in the Netherlands revealed an overall complication rate for hysteroscopy of 0.28%. Diagnostic hysteroscopy had a significantly lower complication rate than that of operative hysteroscopy (0.13% vs. 0.95%). The most frequent surgical complication was

uterine perforation (0.76%). Reported complication rates for hysteroscopic ablation procedures are significantly higher. O'Connor and Magos followed 525 women for up to 5 years after endometrial resection. They reported a 6% incidence of intraoperative complications and a 3% incidence of postoperative complications. They also reported a 15% complication rate in patients who required a repeat ablative procedure. The "Mistletoe" survey led by Overton et al. from the Royal College of Obstetricians and Gynaecologists recorded endomyometrial resection complication rates of 7.2% but only 4% for roller-ball and laser ablations. A prospective trial by Meyer et al. of thermal balloon versus roller-ball ablation reported intraoperative complications in 3.2% of the roller-ball patients but no significant intraoperative complications in the thermal balloon patients. Reported complications include uterine perforation with hemorrhage, laser or electrosurgical damage to the bowel, excessive absorption of distending medium with fluid overload, hyponatremia and pulmonary edema, and persistence of bleeding requiring repeat ablation or hysterectomy. The complication rates reported by Summitt et al. compare favorably with reported morbidity rates for women undergoing hysterectomy, which range from 7% to 15%.

There is concern regarding the potential outcome of pregnancies conceived after endometrial ablation. A literature review by Cook and Seman reports a miscarriage rate of 21.7%, a preterm rate of 26.1%, and a perinatal mortality rate of 11.8%. Of those pregnancies that continued beyond 20 weeks, 35.3% were described as having abnormal placental adherence, including placenta accreta and increta. The hysterectomy rate for this series of patients was 8.9%. These outcomes were attributed to the possible presence of intrauterine synechiae, although in most cases, no direct endometrial cavity assessment was performed.

Another concern has been possible obliteration of warning signs heralding the development of endometrial carcinoma, with subsequent delay in diagnosis. Endometrial ablation procedures usually result in a narrowed tubular uterine cavity without the obliteration seen in Asherman syndrome, but are rarely expected to result in total ablation of all endometrial tissue. Several cases of postablation endometrial carcinoma have been reported by Brooks-Carter et al. and Copperman et al. The cost of endometrial ablation does compare favorably with that of hysterectomy, with hysterectomy reported by Vilos et al. as 58% more expensive when all costs, including lost work time, are considered.

Dilatation and curettage is most useful as a diagnostic technique when it is combined with hysteroscopy. Although D&C will acutely address AUB, it is not a long-term treatment of AUB. Removal of the structurally fragile bleeding endometrium allows restoration of normal hemostatic events, with regeneration of the integrity of the endometrium and restoration of the normal proliferative response. If the patient fails to respond to medical therapy, repeated curettage, or even endometrial ablation, then more definitive therapy, such as hysterectomy, should be considered, taking into account the age of the patient and her desire for future childbearing. It

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has been estimated that 2 million women in the United States are seen annually with reports of excessive uterine bleeding, and approximately 150,000 undergo hysterectomy, which accounts for 20% to 30% of all hysterectomies performed.

In general, the ovulatory type of bleeding has the poorest response to replacement hormonal therapy and the highest incidence of recurrence. Although a hysterectomy can be considered an admission of therapeutic defeat, it is frequently an expeditious method of resolving this refractory and recurrent type of AUB. When bleeding persists after repeated curettage and cyclic hormonal therapy, hysterectomy may be required. If other conditions are present that should be corrected surgically, such as a relaxed vaginal outlet, rectocele, cystocele, or uterine descensus, we recommend vaginal hysterectomy with support of the vaginal vault and repair of the vaginal wall relaxation. When hysterectomy is indicated in premenopausal women younger than 50 years of age, normal ovarian tissue is conserved. In a patient younger than 30

years of age, radical surgical treatment should be strongly avoided; one can almost always control uterine bleeding by repeated curettage or by increasing amounts of cyclic hormone therapy. Today, the availability and use of estrogen and progesterone have changed the need for hysterectomy to treat AUB. Hysterectomy is not indicated in young women but may be indicated in older women when hormonal therapy and curettage have failed. Although curettage may acutely improve bleeding, it is not a long-term therapy.

Blood transfusions are seldom required when AUB is associated with anemia, but they may be given if the anemia is so severe that symptoms are present. Oral iron therapy should be started at the first sign of heavy menstruation to prevent depletion of iron stores, and it should be given for 3 to 6 months after normal hemoglobin and hematocrit levels have been restored in patients with iron deficiency anemia.

## **PERIMENOPAUSAL AND POSTMENOPAUSAL BLEEDING**

When uterine bleeding occurs more than 12 months after the last regular menstrual period, it is defined as postmenopausal bleeding. For a period varying from months to years before menopause, the individual patient may experience irregular patterns of bleeding. Often, the first sign is a shortening of the menstrual interval secondary to premature elevation in FSH, followed by intermittent periods of amenorrhea alternating with heavy bleeding consistent with oligoovulation or anovulation. With this clinical picture, special consideration must be given to ruling out a neoplastic process as the source of the bleeding. The first diagnostic consideration is to ensure that the bleeding originates from the uterus. In elderly women especially, bleeding from the urethra or rectum may be reported as vaginal bleeding. Vaginal or cervical lesions causing the bleeding should be diagnosed readily with careful inspection or biopsy. Cancers of the vagina or cervix or cervical polyps can also be readily diagnosed and appropriate treatment rendered.

When the source of the bleeding is determined to be the uterine cavity, sampling of the endometrium for pathology examination is usually considered to be mandatory. Although D&C at the time of hysteroscopy continues to be a commonly performed procedure for both its diagnostic and short-term therapeutic benefits, office endometrial biopsy can often expedite appropriate evaluation and therapy. Many instruments have been devised for the sampling of endometrial tissue and evaluation of the endometrial cavity. The standard instrument used for many years had been the Novak curette because of the discomfort associated with passage of the Novak curette; newer Silastic curettes have been developed. These have a smaller diameter (3 mm), are flexible, and are often better tolerated by patients. They can be difficult to pass through a truly stenotic cervix because of their pliability. Often, there is an accompanying syringe that attaches and develops effective vacuum pressure to improve the size of the sample obtained. A four-quadrant endometrial biopsy with passes along the anterior and posterior and both lateral walls of the endometrial cavity is recommended for diagnosis of abnormal bleeding. Another potentially useful device not requiring a syringe to develop negative pressure is a disposable plastic tube with a 3.1-mm outer diameter, an aspiration port, and solid plastic obturator at its tip. The obturator fits so closely that its slow withdrawal from the uterine cavity causes sufficient suction to obtain an adequate endometrial specimen in most cases. However, the endometrial surface area sampled is small (5%) and can easily miss polyps, submucous myomas, and endometrial carcinoma that occupies only a small portion of the endometrial cavity. Because of the small aperture of this device and its almost total reliance on suction to obtain a specimen, the architecture of the obtained biopsy may be somewhat distorted.

Vacuum suction curettage has gained some popularity as an office procedure for endometrial sampling that does not require general anesthesia. A small metal or plastic cannula with an outside diameter of 3 mm that has a slightly curved tip and an opening on the concave surface for easier insertion through a small endocervical canal is connected to a plastic collection chamber, which, in newer models, is a large syringe rather than the old pumps or faucets. Several studies have compared the results of suction curettage with those of regular curettage under anesthesia in the same patient. Cohen and colleagues studied 98 patients; in 93, they found identical



histologic patterns with both methods. In five patients, there was no correlation between the results of the two techniques, and none of these had cancer. At the Medical University of South Carolina, Lutz and colleagues found suction curettage to be 98% accurate in evaluating high-risk women with abnormal bleeding for endometrial malignant disease. Recent evidence from Kazandi et al. suggests that although Pipelle biopsies have equivalent diagnostic accuracy with widespread endometrial lesions they provide limited diagnostic accuracy in cases with focal pathologies.

The principal value of an endometrial biopsy is that a formal D&C under anesthesia has been avoided if the removed tissue contains adenocarcinoma. If the cause of postmenopausal bleeding is not identified in a screening endometrial biopsy and the endometrial stripe is greater than 5 mm, a hysteroscopic-directed endometrial sampling is obligatory. In office biopsies of the endometria of more than 20,000 patients of all ages, Hofmeister detected 273 cases of endometrial carcinoma, 32 of which (14.28%) were totally asymptomatic. The endometrial carcinoma detection rate was 1.76% of the total group of 23,202 patients. Hofmeister's routine office endometrial biopsies using a modification of the Novak and Randall curette provide one of the largest clinical experiences of this instrument to date. Unfortunately, only patients who had continued uterine bleeding or who demonstrated an atypical pattern in the office biopsy were subjected to a complete curettage. Therefore, the true-negative and false-negative rate for the Novak type of curette in the detection of endometrial cancer has not been determined accurately. In other studies, summarized by Cohen and colleagues, the accuracy of detection of endometrial cancer by endometrial curettage varied from 76% to 92%. However, a thorough endometrial curettage under

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anesthesia is also not infallible in the detection of endometrial cancer. Bettocchi and colleagues evaluated the diagnostic accuracy of endometrial curettage in 397 patients; D&C failed to detect intrauterine pathology in 62.5% of patients, including four cases of complex hyperplasia, five cases of endometrial adenocarcinoma, and many endometrial polyps and submucous myomas. The use of hysteroscopic-directed sampling may decrease that number.

Vaginal ultrasound has been investigated as a screening tool in patients with postmenopausal bleeding. The average thickness of the postmenopausal endometrial stripe has been reported as  $2.3 \pm 1.8$  mm, with a range of 0 to 10 mm, in a series of 300 asymptomatic women. Twenty-two had endometrial stripes of 5 mm or larger, and all had benign pathology. In a series of 51 cases of postmenopausal bleeding, Nasri and colleagues reported that if the endometrial thickness was less than 5 mm, the pathology would show either inactive or no endometrial tissue. Karlsson and associates reported on 1,168 women with postmenopausal bleeding. Patients with an endometrial echo of less than 4 mm had a sensitivity of 96% and a specificity of 68% for detecting endometrial pathology. If a 5-mm cutoff was used, two endometrial carcinomas would have been missed. In another study by Gull and colleagues, 198 women screened for postmenopausal bleeding had an endometrial thickness of 5 mm or greater. Endometrial sampling diagnosed 36 primary endometrial cancers, one metastatic breast cancer, and three cases of atypical endometrial hyperplasia. Of 163 women with an endometrial stripe of 4 mm or less, only one was found to have endometrial cancer. Other series have shown that an endometrial thickness of greater than 8 mm is an indication for endometrial sampling, regardless of whether there is a report of bleeding. This will detect most, if not all, endometrial cancers. A meta-analysis by Smith-Bindman et al. reviewing the accuracy of transvaginal sonography reported that 96% of women with endometrial cancer and 92% of women with other endometrial diseases had an endometrial echo of greater than 5 mm. The false-positive rate was dependent on the use of hormone replacement therapy, with nonusers having a false-positive risk of 8%, whereas those on hormones had a 23% false-positive rate. Saline infusion sonography can be used to further evaluate patients with thickened endometrial stripes to detect structural problems such as polyps as an adjunct to endometrial sampling. Although the exact indications for patient screening and parameters for follow-up need to be more precisely defined, vaginal ultrasound appears to have promise as a noninvasive method for evaluating the

postmenopausal patient.

Office hysteroscopy using new smaller-diameter flexible or rigid hysteroscopes is growing in popularity because it enables selective biopsy of the areas of visualized endometrium that appear most likely to contain a neoplastic process. A blind endometrial biopsy that reveals benign endometrial histology does not absolutely preclude the presence of a malignant process elsewhere within the endometrium. A neoplastic transformation in the endometrium is often a focal abnormality. Another major advantage of hysteroscopy is the diagnosis of endometrial polyps, submucous myomas, or other sources of bleeding that may not always be identified by endometrial biopsy or conventional curettage. In a series of 110 cases of postmenopausal bleeding, the causes of 95 were identified as endometrial polyps or submucous myomas. Only two cases of early adenocarcinoma were identified. Operative hysteroscopy, endometrial ablation, or both successfully controlled bleeding in most cases of benign disease. In cases of postmenopausal uterine bleeding, the recommended diagnostic procedures may or may not produce a tissue sample of endometrium. If the endometrium is not atrophic, a wide range of histology can be observed. Occasionally, simple proliferative endometrium is found. The endometrium can exhibit simple hyperplasia, more marked adenomatous hyperplasia, or hyperplasia with atypical cells, resulting in a diagnosis of atypical endometrial hyperplasia. Later in the menopausal years, it is not uncommon for the endometrium to have the characteristics of cystic hyperplasia, often referred to in the older literature as "Swiss cheese hyperplasia."

Hormone-induced postmenopausal uterine bleeding can be the result of endogenous or exogenous hormonal effects. The proliferation of endometrium in a patient who is not receiving exogenous hormonal therapy is generally attributed to endogenous production of estrone. Estrone is the peripheral conversion product of the weak androgenic precursor androstenedione (85% from adrenal and 15% from ovary), and its synthesis occurs primarily in adipose tissue. In the absence of exogenous hormonal therapy, one must also exclude the possibility of an estrogen-producing ovarian tumor (granulosa cell tumor).

Management of perimenopausal bleeding in the absence of significant hyperplasia or neoplasia is essentially the same as for AUB in a younger patient. One recently accepted method that in the past was proscribed is the use of low-dose oral contraceptives. The Food and Drug Administration has approved them for patients older than 40 years of age in the absence of specific contraindications, such as hypertension, hyperlipidemia, and smoking. They provide excellent cycle control with a monthly withdrawal bleed and suppression of the endometrium. Oral contraceptives can be continued until an FSH level greater than 40 IU/L during the week of placebo pills confirms ovarian failure. Standard postmenopausal hormone replacement can then be used. A sequential program of 12 days of progestin, 5- to 10-mg medroxyprogesterone acetate, or 5-mg norethindrone acetate on a monthly basis is an alternative and is continued until failure of withdrawal bleeding occurs, indicating the need for estrogen replacement. Endometrial hyperplasia requires a more aggressive progestational regimen. Atypical adenomatous endometrial hyperplasia is considered by most to be the equivalent of an intraepithelial malignancy, and hysterectomy is often advised. Management of several types of endometrial hyperplasia other than atypical adenomatous hyperplasia can generally be accomplished by monthly administration of a progestin such as medroxyprogesterone acetate, 10 mg per day for 12 days, or norethindrone acetate, 5 mg per day for 12 days. Another endometrial biopsy should be obtained within 3 to 6 months to assess for resolution of the hyperplasia. A more aggressive hormonal regimen uses continuous high-dose progestin for 3 to 6 months (i.e., megestrol 20 to 160 mg per day).

Any of the regimens currently in use for postmenopausal hormonal replacement therapy can cause uterine bleeding. Since the WHI, the number of women using postmenopausal HT has markedly decreased, but there is still a role for this therapy in symptomatic women. A summary of the guidelines published by several major medical societies can be found in a recent publication by Dr. Pines. Unopposed estrogen is no longer recommended for postmenopausal hormone replacement in the case of an intact uterus because hyperplasia

develops in 18% to 32% of cases and because unopposed estrogen has an up to sevenfold increased risk of endometrial carcinoma. Cyclic estrogen-progestin regimens significantly decrease this risk to less than 1% with 12 days of progestin. There are numerous dosage regimens for the use of conjugated estrogens 0.625 to 1.25 mg; micronized E<sub>2</sub> 1 to 2 mg; esterified estrogens 0.625 to 1.25 mg; and E<sub>2</sub> patches. Although estrogen

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replacement therapy performs well if used for only 21 to 25 days of the month, there is no clinical reason for its discontinuance, and recent recommendations are to continue it throughout the entire cycle. The progestin regimens are those that have already been outlined. The bleeding that accompanies these commonly used continuous-estrogen and cyclic progestin regimens should occur predictably, at the conclusion of the progestin phase of the cyclic administration. Most investigators of the subject now agree that the predictable and appropriately timed withdrawal bleeding that occurs with these regimens does not require sampling for endometrial histology. As a general rule, just as intermenstrual bleeding during the regular menstruating years dictates investigation and management, so do patterns of postmenopausal bleeding not following an anticipated schedule require investigation and management.

The most important point about the significance of postmenopausal bleeding is its frequent association with gynecologic malignancy, particularly endometrial carcinoma. Although the incidence of malignancy to explain postmenopausal bleeding has decreased in recent decades, diagnostic efforts must carefully consider and rule out possible malignancy by use of appropriate diagnostic procedures, especially careful pelvic examination and uterine curettage. An endometrial biopsy is helpful for the diagnosis of suspected endometrial carcinoma only if the biopsy is positive. The definitive method for obtaining adequate histology for diagnosis is hysteroscopy and D&C.

## CURETTAGE OF THE UTERUS

### Indications and Contraindications

#### STEPS IN THE PROCEDURE

##### Dilatation and Curettage

- Lithotomy position, empty bladder, and sterilely drape perineum
- Thorough exam under anesthesia to evaluate uterine size and position
- Adequate exposure of the cervix with open-sided or weighted speculum
- Assess depth of uterine cavity using a uterine sound
- Curettage of the endocervix using a small box curette
- Dilatation of cervix using Hegar or Hank dilators
- Measure endometrial cavity depth using a sound
- Curettage of anterior, lateral, and posterior walls using a small or medium malleable, bluntly serrated curette

It is important that D&C be performed for the proper indications, be performed correctly to obtain the most useful information, and be performed safely. A curettage performed properly and with aseptic technique involves little risk, but if precautions are disregarded, complications and even death can result.

The chief purpose of curettage of the uterus is the removal of endometrial or endocervical tissue for histologic study of cases of AUB. Although classical curettage of the uterus continues to be a useful procedure, new

practices and instrumentation permit the procurement of endometrium as a screening diagnostic test under many circumstances. Appropriate use of such procedures can reduce significantly the need for operating room curettage. Careful pelvic examination under relaxation anesthesia has been an important adjunctive diagnostic aid to conventional D&C, but the precision and availability of ultrasound and other imaging techniques have brought them to the forefront of importance in diagnosis.

## Outpatient Curettage

Over the years, there have been efforts to lower the cost of D&C by making it an outpatient procedure. Today, D&C is often performed satisfactorily on an outpatient basis or in an ambulatory surgery center. Reports by Sandmire and Austin and by Martin and Rust are among many that record favorable experiences with this procedure.

As mentioned earlier, endometrial sampling today is often performed by biopsy, suction, or D&C as an office procedure. Only if they show frank adenocarcinoma can the outpatient biopsy results be considered definitive. If the histology of the office procedures is negative, a more serious condition has not been ruled out. A further note of caution is that none of the office endometrial sampling methods can ensure the removal of an endometrial polyp. Therefore, endometrial carcinoma in a polyp could be missed, as could a polyp that is a source of benign bleeding. Office sampling techniques are used only as screening procedures; if the results are negative, a more thorough evaluation using hysteroscopy is indicated. Office hysteroscopy can sometimes identify missed pathologies, such as a polyp or a submucous myoma, or to allow directed biopsy of a suspicious endometrium.

Indications for obtaining endometrial histology by one or more of the aforementioned methods include the following:

- Abnormal bleeding at any premenopausal age, especially when not corrected promptly by medical management; in women older than 35 years of age; or if a submucous myoma is suspected (include hysteroscopy or hysterosalpingography),
- Postmenopausal bleeding of any amount, regardless of a finding of atrophic vaginitis, polyp, or urethral caruncle,
- Prehysterectomy in the postmenopausal woman at risk for endocervical or endometrial carcinoma, and
- Postmenopausal vaginal surgery without hysterectomy in women at risk for endometrial pathology.

When office procedures fail to establish the diagnosis, hysteroscopy is the preferred diagnostic method. Unlike blind D&C, it allows for visualization of the uterine cavity and direct biopsies. Hysteroscopy performed under general anesthesia allows for more extensive operative procedures if indicated. Occasionally, new and important pelvic findings will be discovered. In a study of 2,666 women requiring curettage, McElin and colleagues found unanticipated adnexal masses in 30 women during pelvic examination under anesthesia before D&C. Twenty-eight masses were benign, and two were malignant. Even in women who have medical contraindications to anesthesia, office hysteroscopy can be performed with minimal anesthesia. A single curettage will not remove all of the surface endometrium completely from the uterine cavity. Repeated studies have demonstrated the inability of a thorough curettage to remove more than 50% to 60% of the endometrium when the procedure has been performed by experienced gynecologists immediately before a planned hysterectomy. Stock and Kanbour, from McGee Hospital in Pittsburgh, observed that in 60% of hysterectomy specimens studied, less than 50% of the endometrial surface had been removed by a prehysterectomy curettage. They also found 26 cases of endometrial carcinoma that had been classified as clinically normal-appearing tissue

on prehysterectomy curettage; six of these carcinomas were reported as benign on frozen section. These facts and other similar experiences indicate that it is difficult to be certain of the histology of the endometrium by gross



examination of the curetting. If the symptoms warrant curettage, then the endometrium deserves a full histologic diagnosis under hysteroscopic visualization.

Curettage is also performed for bleeding from a cervical stump and is frequently performed as part of a cervical conization to rule out extension of cervical carcinoma into the endometrium. Helmkamp and associates found no evidence of endometrial abnormality in any of 114 curettage specimens removed at the time of 114 cervical conizations. These investigators recommend that curettage at the time of cervical conization should not be performed routinely but should be performed selectively in postmenopausal and perimenopausal patients when the cytology smear shows abnormal glandular cells or when an intrauterine abnormality is suspected.

The chief contraindication to curettage is infection. Acute endometritis and salpingitis are conditions under which curettage should be avoided. If curettage is necessary for removal of infected placental tissue, it should be preceded by a period of parenteral antibiotic therapy adequate to achieve therapeutic tissue levels. Endometritis associated with retained products of conception will remain unresolved until the infected necrotic material is removed. Curettage is also contraindicated when pyometra is present.

### Technique of Curettage of the Uterus

After the patient is anesthetized and placed in the lithotomy position, the bladder is emptied with a catheter. The pelvic organs are examined thoroughly before the patient is prepped and draped. The procedure includes a bimanual rectovaginal-abdominal examination. The examination under anesthesia is one of the most informative features of this operation because it can provide anatomic details of the reproductive tract that are unrecognizable without anesthesia. The vagina and perineum are cleaned with the usual technique.

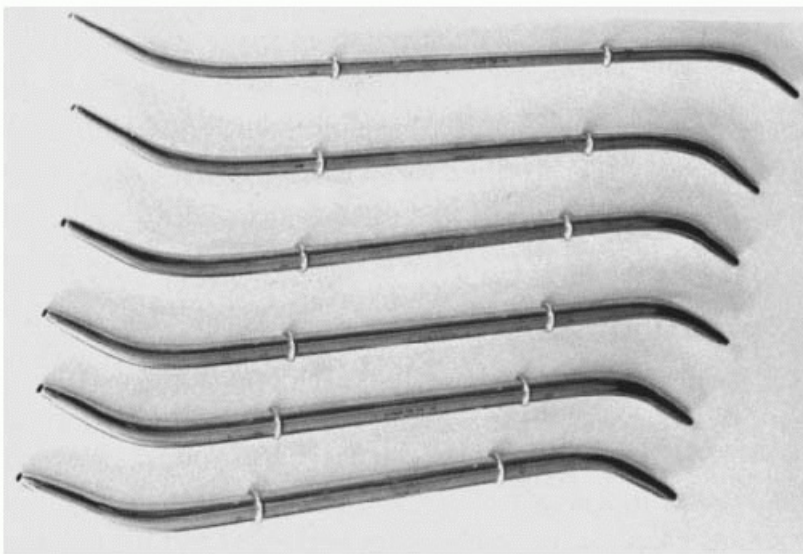
Fractional curettage is an attempt to remove tissue samples from the endocervical canal apart from tissue removed from the endometrial cavity. The cervical canal should be curetted before dilatation of the cervical canal and curettage of the endometrial cavity. The special shape of the small Gusberg curette makes it particularly useful for curetting the endocervix. Differential curettage of the endocervix, separate from the endometrium, is important for diagnosis of endometrial carcinoma that may have extended to the endocervix. All cases of perimenopausal bleeding should be fractionally curetted; this procedure is too often neglected. If the endocervical curettage is not performed, a second fractional curettage is required to determine the anatomic boundaries of endometrial carcinoma. The value of fractional curettage has been questioned, but Chen and Lee and others have emphasized the importance of cervical stromal invasion, rather than the finding of tumor tissue, as the crucial criterion in endocervical curetting affecting staging and prognosis.

The uterine cavity is then sounded to determine its size and to confirm the position determined from examination under anesthesia. The cervical canal is dilated with the Hegar or Hank-Bradley ([Fig. 26.6](#)) dilator. A dilatation to 8 or 9 mm by a Hegar dilator ([Fig. 26.7](#)) is sufficient for the usual diagnostic curettage. A gauze is placed in the posterior vaginal fornix along the posterior retractor so that the blood and the endometrium removed from the uterus can fall on it. Before the curettage is performed, the uterine cavity is explored for endometrial polyps by use of a narrow stone forceps. This forceps can be opened and closed as the tip of the forceps is moved systematically across the dome of the uterus and the anterior and posterior walls. An endometrial polyp can be easily missed with an ordinary curette, and unnecessary hysterectomies have been performed because of supposed persistent

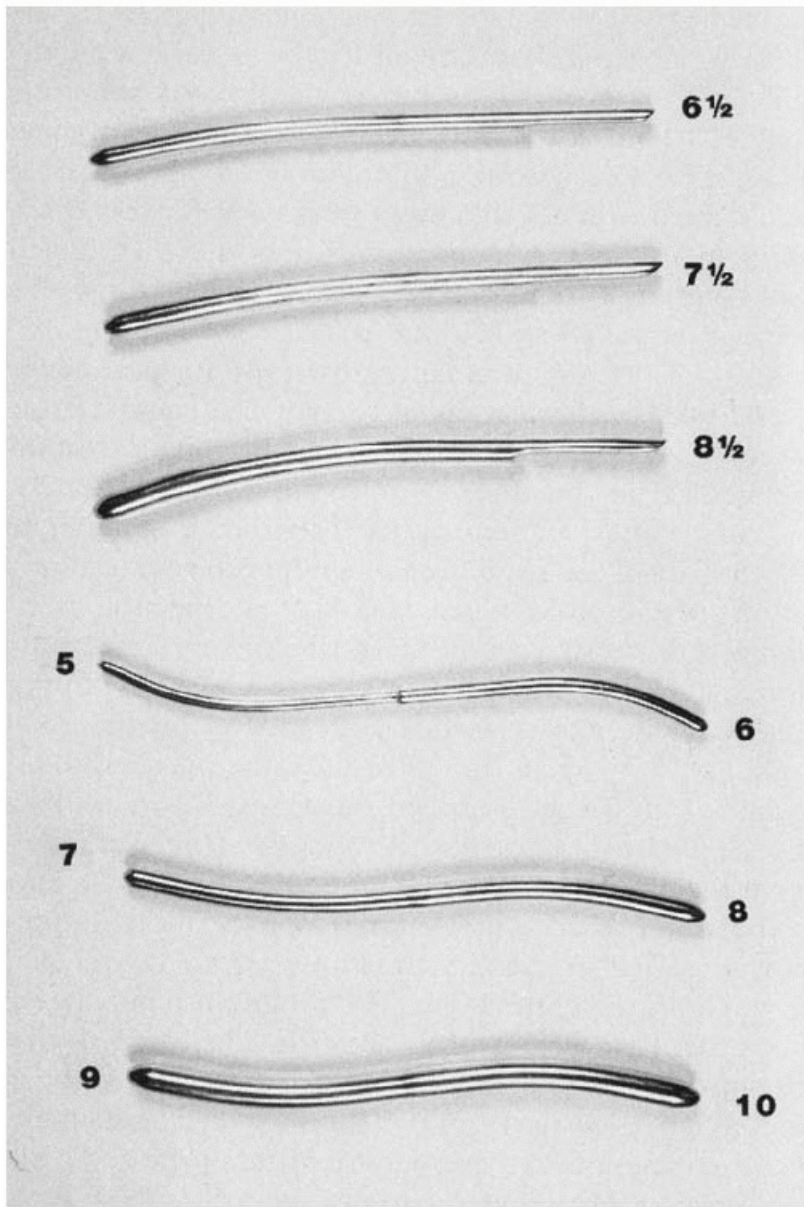
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or recurrent dysfunctional bleeding after curettage ([Fig. 26.8](#)). If polyp forceps are routinely used, such operations can be avoided. It is easier to identify and remove an endometrial polyp if the uterine cavity is explored with the stone forceps before the uterus is curetted. In a 28-month period during which forceps were used routinely at the Johns Hopkins Hospital, Josey found that endometrial polyp was diagnosed 130 times. In 83 of these cases, the polyp was removed by forceps. Although the sessile form of a submucous myoma is

diagnosed easily by noting an irregularity of the uterine wall with the curette, the pedunculated variety, like the endometrial polyp, can escape detection because of its narrow stalk. Removal of pedunculated leiomyoma can sometimes be accomplished with the polyp forceps. A uterine septum can also sometimes be detected with the forceps, but imaging modalities such as saline sonohysterogram and hysterosalpingogram are more accurate diagnostic tests. The procedure is most likely to be diagnostic and therapeutic when it is combined with direct visualization of the uterine cavity through hysteroscopy. A small-sized or medium-sized, malleable, bluntly serrated curette ([Fig. 26.9](#)) is then introduced into the uterus, and the entire uterine cavity is systematically curetted. The anterior, lateral, and posterior walls should be sampled ([Fig. 26.10](#)). The handle of the curette should be held gently, as one would hold a pencil. The instrument is held loosely as it is inserted for the full distance. Pressure is then exerted against the uterine wall as the curette is drawn in an outward direction. Because the instrument is malleable, its curvature can be changed to conform to the contour of the uterine cavity. A uterine “cry,” vibrations felt in the hand holding the curette, is often used as a sign that adequate tissue has been removed. It should be remembered, however, that overly aggressive curettage can lead to scarring of the endometrial cavity.



**FIGURE 26.6** Hank-Bradley dilators in graduated sizes. Note central canal that extends through length of dilator.

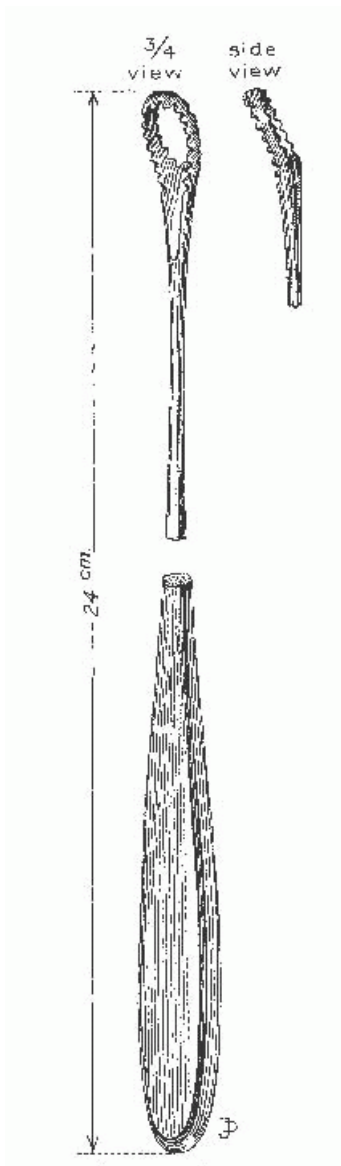


**FIGURE 26.7** Graduated Hegar dilators and “half-size” Hegar dilators.



**FIGURE 26.8** Opened uterus, showing two separate endometrial polyps.





**FIGURE 26.9** Small serrated curette for routine curettage.

The unclotted blood is absorbed quickly by the gauze sponge, leaving the relatively clean endometrium to be placed in a prepared container with appropriate fixative. Again, the curettings should be removed carefully from the sponge with a pair of smooth-tipped forceps and placed immediately in the fixative. The curettings should be examined carefully at this time for fatty tissue or other unusual tissue.

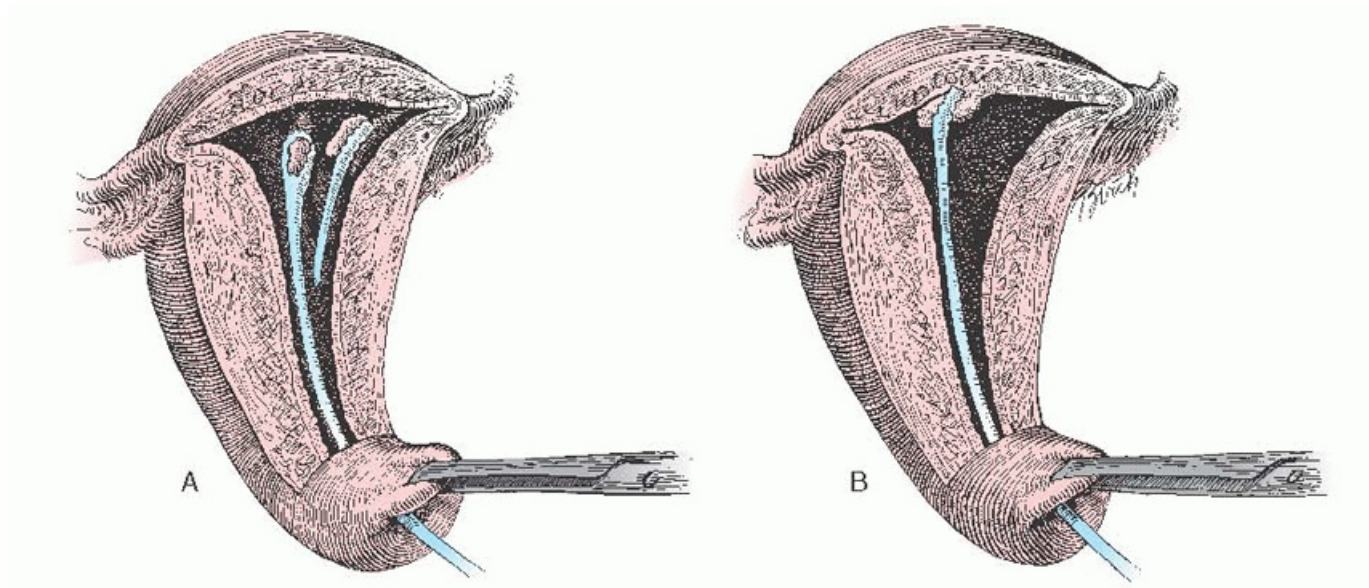
When curettage is performed as a curative measure for removal of placental tissue, a large, blunt, smooth curette is used to lessen the possibilities of perforation and endometrial sclerosis. The larger and softer the uterus, the larger the curette should be and the more care one should exercise to avoid these complications. When large masses of placental tissue are present, ovum forceps are most useful when used in conjunction with the curette. High-vacuum suction is now used almost routinely for placental tissue removal.

Routine blind biopsy of the cervix is usually unrewarding if a negative cytologic smear has been obtained and there is no suspicious cervical lesion. A blind biopsy of the cervix at the time of curettage should not be performed unless an abnormal lesion is present. If a gross lesion is seen, directed biopsy of the lesion is indicated.

### **Complications of Cervical Dilatation and Uterine Curettage**

If the position and the consistency of the uterus are carefully observed on bimanual examination under anesthesia before curettage is begun, perforation will rarely occur. Special care should be exercised with a

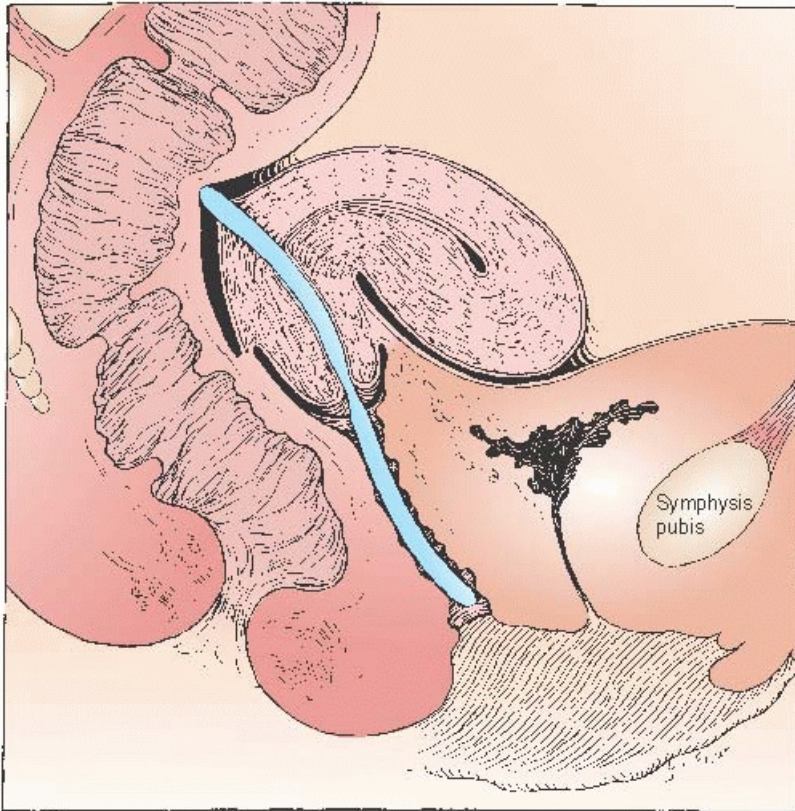
retroflexed (**Figs. 26.11** and **26.12**). With cervical stenosis, pregnancy, or intrauterine malignancy, perforation is more likely. The postmenopausal atrophic uterus can be perforated with only slight force applied to the uterine sound or the curette. Perforation is discovered when the sound or the curette fails to encounter resistance where it normally should, as judged by the palpated size of the uterus and initially measurement of the endometrial cavity by uterine sound. Abdominal ultrasound visualization of the uterus, cervix, and endocervical canal, which may require a distended bladder, can be useful in guiding the passage of either a dilator or a curette through the endocervical canal into the endometrial cavity in difficult cases. Ghosh and Chaudhuri found misoprostol in a dose of 400 µg twelve hours prior to the procedure can facilitate cervical dilation.



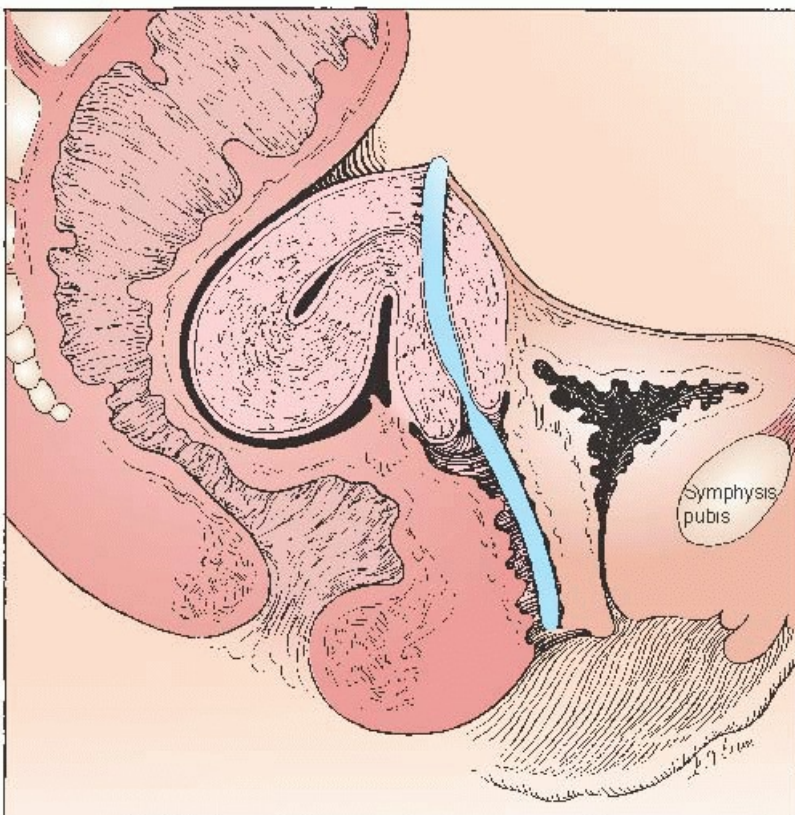
**FIGURE 26.10** Method of curetting the uterine cavity systematically. **A:** The anterior, posterior, and lateral walls of the cavity are curetted systematically. **B:** The top of the cavity is then curetted thoroughly.

Perforation by the uterine sound or cervical dilator causes less damage than perforation by the sharp curette or suction cannula. Sharp curettage for legally induced abortion has a major complication rate that is two to three times higher than that for suction curettage, according to Grimes and Cates. The two principal dangers of uterine perforation are bleeding and trauma to the abdominal viscera. Lateral perforation through the uterine vessels is especially dangerous from the standpoint of intraperitoneal hemorrhage and broad ligament hematoma formation. Damage can occur to the bowel, omentum, mesentery, ureter, and fallopian tube. Perforation of the anterior or posterior wall of the uterus by a small curette in performing a diagnostic curettage is usually not a serious accident. However, it is usually necessary to discontinue curettage. One must

watch carefully for signs of hemorrhage or infection. If signs of hemorrhage develop, the abdomen should be opened and the uterine wound sutured. If signs of infection occur, broad-spectrum antibiotics should be given. If a pelvic abscess develops, the abscess should be drained if possible. As described by Chappel and colleagues, this can sometimes be accomplished under radiographic guidance. Serious hemorrhage or infection occurs only rarely. When serious damage from perforation is suspected, laparoscopy can be performed to assess the extent of the damage and the needed repair. According to MacKenzie and Bibby, complications occurred in 1.7% of cases of D&C. McElin and colleagues reported that 0.5% of cases had postoperative febrile morbidity after D&C. Uterine perforation occurred in 0.63% of cases.



**FIGURE 26.11** Perforation of the acutely anteflexed uterus. The uterus was thought to be in retroposition, and the Hegar dilator was erroneously directed posteriorly.



**FIGURE 26.12** Perforation of the retroflexed uterus. The uterus was thought to be in anteversion, and the Hegar dilator was erroneously directed anteriorly.

One should be absolutely certain that the endometrial cavity has been entered when D&C is performed for postmenopausal bleeding. A relatively stenotic internal cervical os and a fear of uterine perforation can prevent



entry into the uterine cavity above the internal cervical os, resulting in failure to curette the uterine cavity and consequent failure to diagnose the cause of the bleeding. Again, ultrasound can be a valuable tool for confirming placement of the curette tip in the endometrial cavity. Many office hysteroscopes are small enough in diameter that they can be safely used in patients with cervical stenosis. It is also possible to use laminaria or misoprostol to facilitate cervical dilatation.

Perforation of a pregnant uterus is a more serious complication than is perforation of the nonpregnant uterus. First, there is the requirement that all remaining pregnancy tissue be completely removed to prevent sepsis. To accomplish this blindly when there is a defect in the uterine wall is unsafe. Second, the pregnant uterus is a much more vascular organ than is the nonpregnant uterus, and intraperitoneal bleeding can be profuse without significant external bleeding. Third, it often is difficult to be certain when the perforation occurred. If a highvacuum suction Vacurect has passed through the myometrium and the vacuum has been activated, major bowel injury can be present. These considerations have led to the following protocol for D&C of the pregnant uterus:

1. Never activate the vacuum suction if there is any question about the safe location of the Vacurect within the uterine cavity.
2. Laparoscope any pregnant uterus that is possibly perforated. With the laparoscope in place, a second operator can evacuate remaining placental tissue while the laparoscopist monitors safety. Many perforations in which no other visceral damage has occurred are fundal. If laparoscopic observation confirms that bleeding is minimal, the perforation can be managed conservatively with antibiotics and serial hematocrit determination for 24 to 48 hours. If there is no evidence of continued bleeding or developing infection, the patient can be discharged.
3. During laparoscopy, if there is any evidence of intestinal injury or any suspicion of such injury, or if bleeding is significant, then laparotomy is mandatory. Unfortunately, bowel injury by high-vacuum suction may require bowel resection and anastomosis.

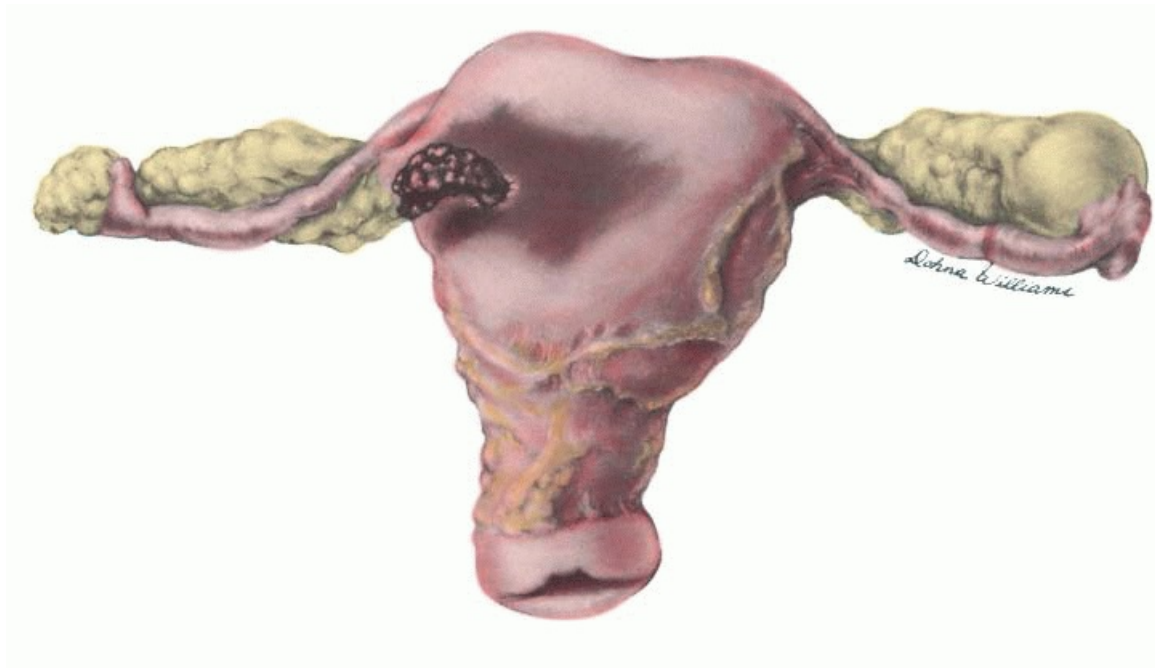
**Figure 26.13** shows a uterus removed immediately after a perforation because of intraperitoneal bleeding. Word analyzed 70 accidental uterine perforations. Among these, an unplanned hysterectomy was performed on seven unprepared patients. In none of these cases did the intraperitoneal findings indicate the need for hysterectomy. In fact, hysterectomy compounded the surgical error. Fifty-five patients were treated conservatively, and only one developed a complication, in the form of a pelvic abscess that was drained by colpotomy. Forty-one of the 70 perforations occurred in postmenopausal women.

When a large, boggy, postabortion or puerperal uterus is perforated by a large curette or placental forceps in removing placental tissue, there is more danger of hemorrhage, infection, or injury to bowel. The treatment protocols and the procedures for these serious complications are discussed elsewhere in this textbook.

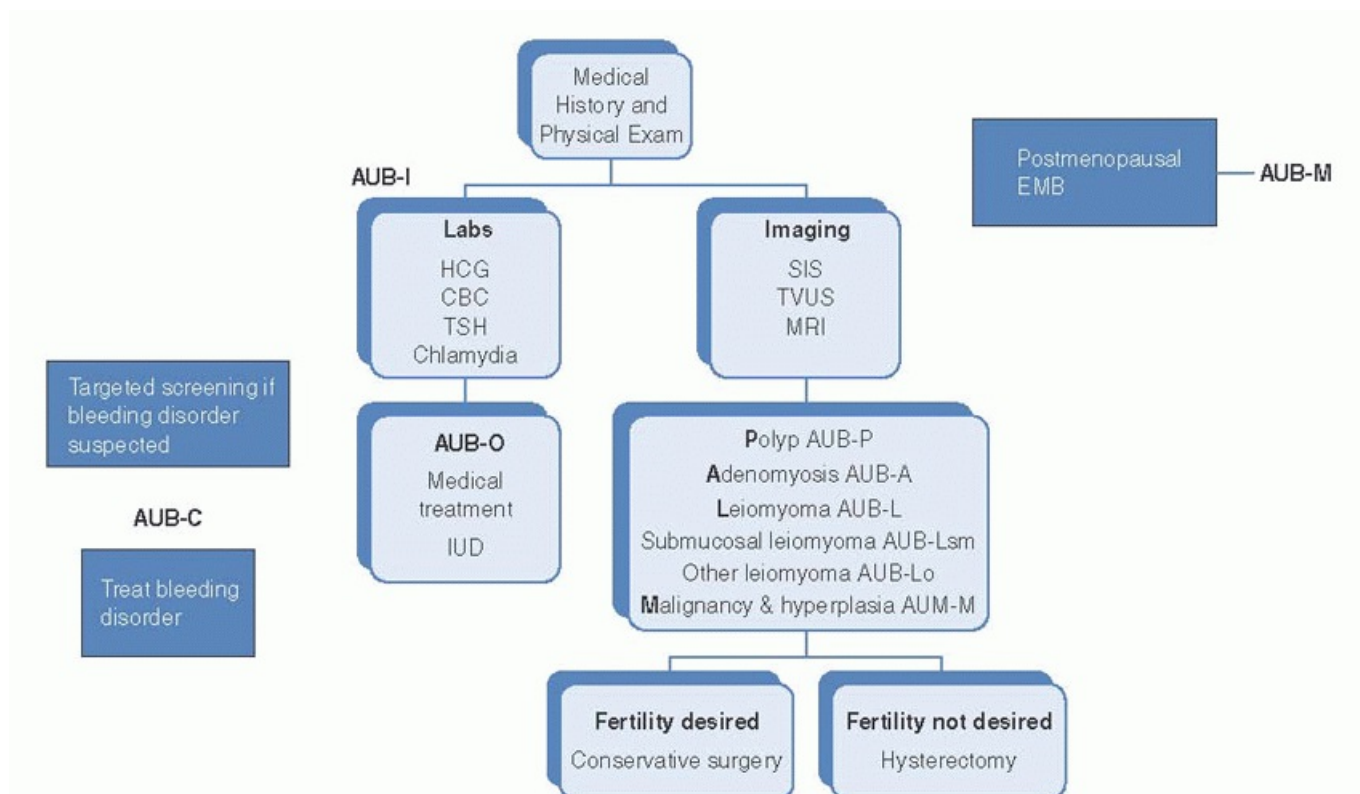
Asherman syndrome is a pathologic condition of intrauterine adhesions that can cause secondary amenorrhea, other menstrual irregularities, infertility, or recurrent abortion. Numerous investigators have shown a strong association between puerperal D&C and the formation of synechiae that can partially or completely obliterate the endometrial cavity. No incidence figures are available because no prospective studies have been performed, but factors other than pregnancy that increase the risk of endometrial sclerosis after D&C are infection, scant endometrium that exposes the basalis to trauma, and a hypoestrogenic state. Rarely, significant synechiae are seen in the absence of an antecedent

curettage. Cases have been reported after severe endometritis, tuberculosis, myomectomy, and cesarean section. Diagnosis is made by clinical history, hysterosalpingography, or hysteroscopy. Therapy requires lysis of adhesions by repeat curettage or, preferably, by hysteroscopic scissors.





**FIGURE 26.13** Result of uterine perforation. Specimen removed directly after perforation.



**FIGURE 26.14** Diagnostic evaluation and treatment of AUB.

Patency of the uterine cavity is maintained with an intrauterine device or balloon catheter, and endometrial regeneration is stimulated by oral estrogen therapy. Women with synechiae are significantly more likely to have placental abruption (2.1% vs. 0.6%), premature rupture of membranes (5.5% vs. 2.3%), and cesarean delivery for malpresentation (5.1% vs. 3.0%). In a recent review of 296 pregnancies with uterine synechiae and over 65,000 pregnancies without synechiae, Tuuli and colleagues did not find a significant increase in placenta previa, fetal growth restriction, stillbirth, and preterm delivery.

This chapter has reviewed normal menstruation, the pathophysiology underlying AUB, the evaluation of AUB, and current treatment modalities. It concludes with a detailed description of the technique of dilatation and

curettage and management of complications of this procedure. Despite emerging medical and surgical therapies, AUB remains a common medical problem among women. An organized approach to the diagnosis and treatment of this problem is critical to the successful management of AUB. **Figure 26.14** provides an algorithm for the diagnosis and evaluation of AUB.

## BEST SURGICAL PRACTICES

- Although hysteroscopy is the gold standard for evaluating endometrial cavity pathology, SIS has comparable sensitivity and is less invasive and less expensive.
- Historic data showed higher amenorrhea rates with endometrial ablation using endomyometrial resection. However, newer techniques of hydrothermablation, radiofrequency current, and microwaves have comparable amenorrhea rates. Hydrothermablation has the advantage of visualization of the endometrial cavity, radiofrequency ablation does not require endometrial pretreatment, and microwave endometrial ablation has been reported to be successful in the presence of small submucous myomas.
- Endometrial sampling can be done by Pipelle, four-quadrant endometrial biopsy, or formal dilatation and curettage (D&C). All of these techniques can miss significant lesions, and the concurrent use of vaginal ultrasonography or SIS will improve sensitivity.
- Hysteroscopy is a valuable adjunct to D&C, particularly in the patient at higher risk for focal endometrial pathology that might be missed on endometrial sampling.
- Abdominal ultrasound guidance may reduce the risk of complications (e.g., perforation during difficult cervical D&C, such as in the stenotic postmenopausal patient or in the case of a large uterus).

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