

Chapter 7

Abnormal Uterine Bleeding



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1 Introduction

Abnormal uterine bleeding (AUB) is defined as bleeding of abnormal duration or quantity usually defined as above 80 ml/month [1]. AUB is one of the most frequent gynecological complaints, and its prevalence is estimated to occur in 20% or more of women [2].

During the past, descriptive terms have been used to characterize AUB—menorrhagia for heavy uterine bleeding, metrorrhagia for bleeding between periods, polymenorrhea and oligomenorrhea for frequent bleeding or infrequent bleeding (respectively). In 2011, the International Federation of Gynecology and Obstetrics (FIGO) [3] introduced a new nomenclature for AUB for non-gravid reproductive-aged women, known by the acronym PALM-COEIN. This system divides the etiologies for AUB to two groups: (1) Structural causes: PALM (Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia); (2) Nonstructural causes: COEIN (Coagulopathy, Other, Endometrial, Iatrogenic, Not yet classified).

Initial evaluation should assess the source and clinical features of the bleeding and exclude organic causes for the bleeding such as fibroids, polyps, carcinoma of cervix or endometrium, coagulation defects, and systemic disease. As the endometrium is a hormonal sensitive tissue, progestogens are a significant factor in treatment. As outlined in other chapters, the choice of hormonal (progestogen) or

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surgical therapy varies according to the diagnosis, the patient's needs and fertility desire. This chapter will discuss the different types of progestogen in use for AUB as well as other treatment modalities.

2 Physiology of Menstruation

Lockwood [4] has given a full account of the pathophysiology of menstruation and the changes in AUB. Briefly, following menstruation, repair of the functional layer takes place. Stem cells in the endometrial stratum basalis proliferate, thus producing a new functional layer under the influence of estrogen secreted by the ripening follicle. The endometrial epithelial and stromal cells proliferate. The stromal cells express vascular endothelial growth factor (VEGF) which induces angiogenesis [5] and the endothelial cells express angiopoietin-2 (Ang-2) [6]. In the secretory phase progesterone produced by the corpus luteum induces changes in the endometrium. Around the new blood vessels, progesterone augments expression of Angiopoietin-1 (Ang-1), from the stromal cells. Ang-1 stabilizes the vessels and blocks further angiogenesis by an anti-mitotic action [7]. The anti-mitotic action also prevents further stromal proliferation and is akin to the anti-mitotic action which is used therapeutically in endometrial cancer (see Chap. 11). Progesterone also induces tissue factor (TF) mRNA and protein in the stromal cells [8]. TF is a receptor for coagulation factor VII and its active form, factor VIIa. TF initiates the clotting cascade, The cascade eventually leads to fibrin production. Decidualized stromal cells continue expressing TF throughout pregnancy [9] leading to the increased tendency to thrombosis in pregnancy. Progesterone also induces a second hemostatic protein, plasminogen activator inhibitor-1 (PAI-1). In addition to its anti-fibrinolytic properties PAI-1 restrains trophoblast invasion [10]. Hence, the luteal phase is associated with hemostatic, anti-fibrinolytic and antiproteolytic properties.

In the absence of pregnancy, luteal regression leads to progesterone withdrawal. The falling progesterone level leads to reduction of TF and PAI-1 expression [11]. When the falling level of progesterone reaches a threshold, the spiral arteries in the endometrial stratum basalis tightly coil and constrict. The vasoconstriction leads to ischemia and necrosis in the functional layer.

Progesterone also inhibits expression of metalloproteinases 2, 3 and 9 (MMP-2, 3 and 9) expression. Progesterone withdrawal augments their expression by endometrial stromal cells. Progesterone withdrawal is also associated with up-regulation of the neutrophil and macrophage chemoattractants, interleukin-8 (IL-8) and macrophage chemoattractant protein-1, respectively [12]. Thus, progesterone withdrawal is associated with increased MMP expression and chemokines which promote leukocyte infiltration which add to the proteolytic milieu, promoting menstrual bleeding and tissue sloughing. As the spiral arteries relax, there is bleeding

into the necrotic endometrium which, together with the chemical changes in the endometrium lead to menstruation. After progesterone withdrawal, there is an increase in prostaglandin (PG) synthesis and a decrease in PG metabolism [13]. PG synthesis via COX-2 is particularly relevant in the vascular compartment, since this provides an explanation for the action of non-steroidal anti-inflammatory agents in the treatment of menstrual disorders including heavy and painful periods. Moreover, prostaglandin E (PGE) synergises with IL-8 to increase capillary permeability, which would facilitate the efflux of leucocytes into the surrounding tissues [14].

2.1 Pathophysiology of Anovulatory Bleeding

Anovulatory AUB is usually seen in adolescents and premenopausal women. In both cases there is bleeding from an endometrium which has been stimulated by estrogen, without progesterone modulation. In adolescents, the unopposed estrogen is often due to immaturity of the feedback mechanisms in the hypothalamic-pituitary-ovarian axis. There are various possibilities. If the negative feedback requires only a certain amount of estrogen to inhibit FSH secretion, but the estrogen level never reaches high enough levels to release LH. Falling FSH levels will lead to follicular degeneration and falling estrogen levels. Hence, the endometrial shadow will be thin on ultrasound, and bleeding may be irregular in occurrence with polymenorrhea or acyclic bleeding. However, if the negative feedback requires higher than normal levels of estrogen to inhibit GnRH release, the excess levels of unopposed estrogen may lead to hyperplasia and prolonged cycles (oligomenorrhea) and subsequent prolonged heavy bleeding. Again, there is no positive feedback and LH release.

In the perimenopause, estrogen production is low compared to the reproductive years. Prolonged exposure to unopposed estrogen may also lead to endometrial hyperplasia, and prolonged heavy bleeding.

The mechanism of AUB in anovulation is due to estrogen breakthrough or withdrawal alone. There are none of the stabilising effects of constantly increasing estrogen levels or of post-ovulatory progesterone. While VEGF and Ang-2 are produced there is not enough Ang-1 to stabilise the vessels and block excess angiogenesis. There is no TF or PAI-1, hence local blood clotting is sub optimal as is the anti-fibrinolytic effect of PAI. When estrogen levels stay stable or fall, the endometrial lining cannot be maintained as it is estrogen dependent. In the absence of progesterone, there is no orderly constriction of the spiral arterioles, and no orderly necrosis of the functional endometrium. The bleeding therefore occurs from excess of fragile blood vessels, with suboptimal thrombosis to stop the bleeding, and possibly excessive fibrinolysis.

3 Diagnosis of AUB

The causes of AUB vary by age. In adolescents, anovulatory cycles, coagulopathies, infections and complications of pregnancies are the most common causes. During the reproductive years anovulation is still a common issue, but there may be other causes such as hormone imbalances induced by contraceptives, structural problems as fibroids, adenomyosis and endometrial polyps. In the perimenopausal woman anovulation is again very common, structural issues such as fibroids are still relevant but endometrial hyperplasia and cancer become more prevalent. The common causes in the postmenopausal woman are vaginal, and endometrial atrophy and complications of hormonal replacement therapy and cancer.

The clinical management of AUB is dependent on the diagnosis. History, examination and diagnosis may differ according to the patient's age. In the adolescent, the likelihood of organic disease such as malignancy is low. Clinical abdominal examination usually gives little information as to cause, and if the adolescent is a virgin, vaginal examination is inappropriate. Consequently, if imaging is normal, there is probably little need to rule out organic disease. However, in the perimenopausal patient, the chance of organic disease is higher, and there is a need for clinical examination to assess uterine size, speculum examination of the cervix, and cervical cytology to exclude malignant changes. Additionally, clinical examination is insufficient, imaging is almost mandatory and even more invasive diagnostic techniques such as endometrial biopsy may be indicated. In the reproductive years, pregnancy should be excluded.

In addition, it must be borne in mind that the patient presents for consultation, because the amount of bleeding seems abnormal for her. There may not necessarily be more than 80 ml of bleeding, but it is necessary to accept the patient's subjective distress at an abnormally perceived bleeding pattern. A quantitative estimate of the amount of bleeding can be obtained by a pictorial blood loss assessment chart. The chart requires that the patient uses a points system to quantify the amount that pads or tampons are soaked in blood, and the number of days of bleeding. However, pictorial blood loss assessment chart is often difficult to apply in clinical practice. Recently, smartphone applications have become available, in which the patient can record the amount of bleeding.

3.1 *Imaging*

Ultrasound, Hysteroscopy, and sonohysterography are used to image the uterus. MRI can also be useful, but is not a primary modality for assessing AUB. These imaging techniques are invaluable for making a diagnosis and directing treatment.

3.1.1 Ultrasound

The first-line modality for pelvic imaging in a woman with AUB is the transvaginal ultrasound (TVUS). In cases where TVUS is inappropriate (virgin patient) or when assessing a large finding (ovarian or uterine) the use of transabdominal US might be beneficial. Ultrasound can detect endometrial thickness, small submucous myomas, adenomyosis, polyp, etc. Figure 7.1 shows a sonogram of an atrophic or hypoplastic endometrium. Figure 7.2 shows a sonogram of endometrial hyperplasia. The ultrasound examination is also used to confirm or refute a diagnosis suspected on the basis of abnormal findings at palpation (e.g. uterine intramural or subserous myomas, or adnexal masses). Ultrasound assessment should also include examination of the adnexa and the urinary bladder, as abnormal bleeding may be explained by a hormone-producing ovarian tumour or a tumour in the urinary bladder. Doppler ultrasonography may provide additional information for characterizing endometrial and myometrial abnormalities, particularly arterio-venous malformations.

If a polyp, adenomyosis or leiomyoma are found, the treatment is surgical or interventional (uterine artery embolization for uterine fibroids or magnetic resonance guided high focus ultrasound for uterine fibroids and adenomyosis) and therefore outside of the scope of this chapter. If no abnormalities are found, endometrial biopsy should be considered.

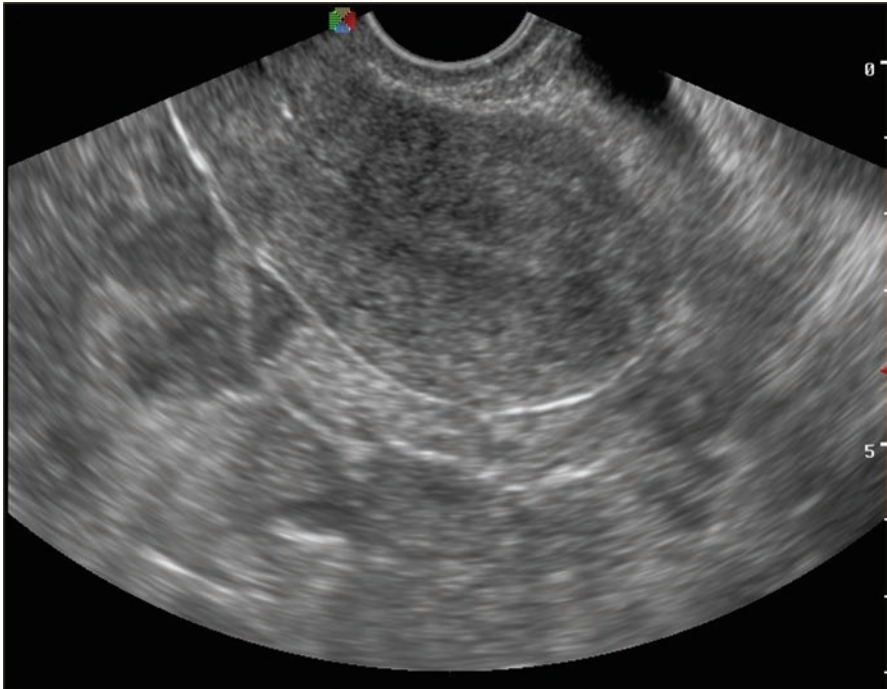


Fig. 7.1 Endometrial atrophy. The endometrial shadow can be seen as a thin faint line

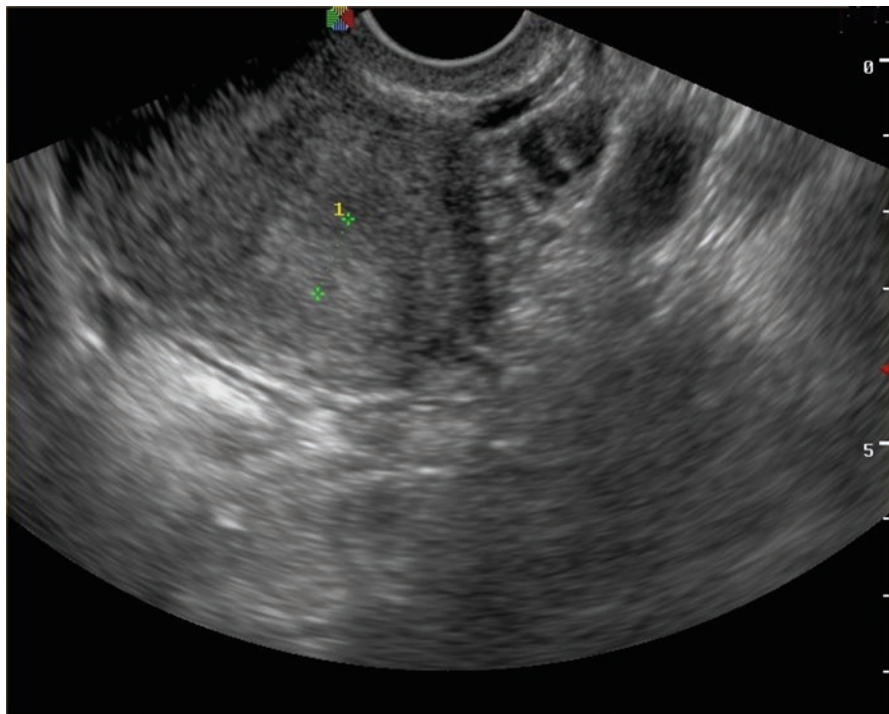


Fig. 7.2 Endometrial hyperplasia. The thickened endometrial shadow can be seen between the two calipers

Doppler flow studies can be added to diagnose arterio-venous malformations and to detect neovascularization, which is of importance in diagnosing malignancy.

3.1.2 Hydrosonography

Hydrosonography is also known as saline-contrast sonohysterography, saline infusion sonography (SIS) or sonohysterography. SIS clarifies the presence of focal lesions protruding into the uterine cavity [15]. If no focal lesions are present in the uterine cavity, the odds of malignancy decrease 20-fold, and the odds of any endometrial pathology decrease 30-fold [16]. A smooth endometrium at SIS is a strong sign of normality. Three dimensional hydrosonography constitutes an improvement in the imaging abilities of SIS, and has been shown to be superior to the older, 2D technique [17].

As most focal lesions cannot be removed, or only be partially removed by blind endometrial sampling, such as pipelle biopsy, or dilatation and curettage, focal lesions should be hysteroscopically resected under direct visual control.

3.1.3 Magnetic Resonance Imaging (MRI)

MRI is not generally recommended as a first-line procedure for investigating AUB. MRI is a good second line procedure if ultrasound reveals a bulky, polymyomatous uterus, or if adenomyosis is suspected. MRI has the advantage of distinguishing between myomas, sarcomas, and adenomyosis. Therefore, MRI can also optimize treatment strategy regarding the use of major surgery, or minimally invasive procedures. MRI can also provide a diagnostic assessment of the endometrium when the uterine cavity is inaccessible [18].

3.1.4 Hysteroscopy

Diagnostic hysteroscopy can diagnose endometrial focal lesions, such as polyp, retained products of conception, caesarean section niche, etc. and atrophy and hyperplasia. Hysteroscopy also has the advantage of allowing a targeted biopsy to be taken, particularly in focal lesions which may be missed by blind endometrial sampling techniques. The likelihood of endometrial cancer diagnosis after a negative hysteroscopy result is 0.4–0.5% [19]. The biggest advantage of hysteroscopy over the other modalities is the possibility to treat at the same procedure, and not merely to diagnose. The European guidelines [20] suggest that hysteroscopy is a second line procedure when ultrasound suggests a focal lesion, when biopsy is not diagnostic, or as an operative procedure if medical treatment fails after 3–6 months.

4 Biopsy

Histological examination is considered the gold standard for making a diagnosis of uterine pathology. Endometrial sampling for the diagnosis or exclusion of mostly hormonally induced endometrial changes (hyperplasia or endometrial cancer) is most often performed with a pipelle. The biopsy also may provide information about the hormonal status of the endometrium. An important limitation of pipelle biopsy is that the pipelle samples an average of only 4% of the endometrium with a reported range of 0–12% [21]. Usually a polyp is an incidental finding during endometrial sampling and is most often not entirely removed by pipelle.

Classically, endometrial sampling was performed by dilatation and curettage (D&C). Pipelle biopsy has replaced D&C, as pipelle biopsy is an office procedure, thus less invasive and less expensive than D&C. In addition, pipelle biopsy does not require the general anesthetic necessary for D&C. Additionally, D&C has been reported to lack the ability to identify uterine focal lesions [22], and blind excision of focal lesions by curettage may be incomplete. Both, D&C and pipelle biopsy show similar success rates for detecting endometrial pathology. The biggest disadvantage of these two techniques is diagnosing focal lesions [23] where hysteroscopy might be indicated.

The question arises as to when sampling is indicated. In the adolescent, there is little place for biopsy, unless absolutely necessary. Goldstein, [24] summarised five large prospective studies in women with postmenopausal bleeding. An endometrial thickness of ≤ 4 mm on transvaginal ultrasound with bleeding was associated with a risk of malignancy of 1 in 917 (3 cancers in 2752 patients). Goldstein concluded that in postmenopausal bleeding, biopsy is not indicated when endometrial thickness is ≤ 4 mm. Furthermore, if biopsy is performed in patients with a thin endometrium, it is most likely that no tissue would be obtained for histology. In a study of 97 consecutive patients with post-menopausal bleeding evaluated by endometrial biopsy, only 82% of the patients with an endometrial thickness ≤ 5 mm ($n = 45$) had a successful Pipelle biopsy completed, and only 27% of them produced a sample which was adequate for diagnosis. The results on postmenopausal women can be extrapolated to premenopausal women. However, in women with endometrial hyperplasia, endometrial sampling is indicated, as there is a high possibility of malignancy.

Endometrial sonographic thickness as an indicator of the need for biopsy is problematic in premenopausal women with AUB, as endometrial thickness changes throughout the menstrual cycle. In our hands, the use of hormonal assessment prior to endometrial sampling has proven to be very clinically useful: determination of blood estradiol, progesterone and beta-hCG levels prior to endometrial sampling can avoid sampling of a pregnant or postovulatory endometrium and allow re-assessment of the ultrasound findings and endometrial thickness in view of the hormonal state of the patient.

5 Bleeding Dyscrasias

Bleeding diatheses generally present as heavy menstrual bleeding commencing at menarche and are present in 10.7% of patients with HMB compared to 3.2% of control women. Von Willebrand's disease is the most prevalent defect associated with HMB with a prevalence of 5–20% [25]. Screening includes activated partial thromboplastin time (aPTT) and ristocetin cofactor assay. Treatment consists of combined hormonal contraceptives which presumably induce TF and PAI-1 levels to compensate for the hemostatic defect.

6 Principles of Treatment

Treatment has a number of objectives: to lessen or stop the bleeding, and to provide long term relief. AUB due to a structural problem (polyp, adenomyosis, and leiomyoma) can be treated surgically. Medical management of endometrial cancer has

been described in Chap. 12. The primary goal of medical therapy should be to stabilize and heal the damaged endometrium with estrogen to provide initial haemostasis, followed by combined estrogen/progestogens for endometrial stability and induction of a menstruation-like withdrawal bleeding. The induced bleed may be stronger than normal menstruation, due to a medical “curettage” of a thickened endometrial layer. However, the induced bleed is usually limited in time, especially if hormonal therapy is continued afterwards. This basic plan of action should be modified according to the patient’s needs, desire for fertility, anemia, endometrial thickness etc. In addition to hormonal therapy, other medical treatment modalities are available such as NSAIDs, tranexamic acid, and receptor modulators. Some specific modifications are listed below.

6.1 Acute Uterine Bleeding

In acute AUB hemodynamic stability should be assessed and a pregnancy test performed. Uterine curettage is the first line therapy when dealing with profuse bleeding and hemodynamic instability. But in most cases the medical situation allows the physician to initiate treatment with hormonal preparations.

6.1.1 High Dose Intravenous Estrogen

Intravenous conjugated equine estrogen (CEE) is approved by the US Food and Drug Administration (FDA) for the treatment of acute AUB. The mechanism of action of the estrogen in these cases is the rapid growth of endometrium over a denuded epithelial surface [26].

IV conjugated equine estrogen (25 mg in each dose, can be repeated after 3–5 h if necessary) has been reported to stop bleeding in 72% of patients within 8 h of administration compared with 38% of participants treated with a placebo [27]. An antiemetic is often required with this regimen. Little data exist regarding the use of IV estrogen in patients with cardiovascular or thromboembolic risk factors, hence, these patients might not be candidates for high dose estrogen treatment.

If the bleeding stops, the IV treatment should be stopped, and oral maintenance treatment should be started with progesterone treatment or combined oral contraceptives, in order to convert the endometrium to a secretory form. Cycling with progestogen should be maintained for 3 months. If the bleeding does not subside after 8 h, surgical intervention may be required. The simplest form of intervention is insertion of a Foley catheter, and expansion of the balloon to cause tamponade. Tamponade can be followed by dilation and curettage if not previously performed. In very rare cases, when all other treatment fails to stop profuse bleeding, hysterectomy might be indicated.

6.1.2 Hemodynamically Stable Patients

In hemodynamic stable patients, hormonal treatment is the preferred treatment method. High dose oral estrogen may be used to cause rapid endometrial proliferation with conjugated equine estrogen 2.5 mg up to four times a day. The dose can be reduced to two times a day when the bleeding becomes moderate. This regimen is given for up to 21–25 days. After the bleeding subsides treatment with progestogen should be administered e:g Medroxyprogesterone acetate (MPA) 10 mg a day. An alternative form of treatment is high dose combined oral contraceptive. If high dose oral contraceptives are used a dose of three pills per day may be required with the resulting side-effects of large doses of hormones. Munro et al. [28] compared the results of oral contraceptives three times daily for 1 week with MPA administered three times daily for 1 week. Bleeding stopped in 88% of women who took OCs and 76% of women who took MPA within a median time of 3 days. Other means of hormonal contraception such as the vaginal ring or patches cannot be used for the treatment of acute AUB, since the effective dosage is not predictable.

High dose progestogens can be used as sole agents in acute AUB. Treatment with progestogens is mainly effective in patients with anovulation. Progestogens inhibit further growth of a thickened endometrium and support estrogen primed endometrium. However, if bleeding comes from a denuded endometrium, progestogen treatment will probably be ineffective. MPA can be given up to 20 mg three times daily for a week or norethisterone acetate (NETA) can be given in doses up to 40 mg daily in divided doses until bleeding stops and then tapered down [29]. Another treatment regimen for acute AUB is depo-medroxyprogesterone acetate 150 mg given intramuscularly followed by MPA 20 mg given orally thrice daily for 3 days [30]. This treatment stopped bleeding within 5 days in all 48 women enrolled in a pilot study. Study participants reported infrequent side effects and high satisfaction.

6.2 *Abnormal Uterine Bleeding in Adolescents*

The aim of AUB treatment in adolescents is to stop bleeding, prevent or reverse anemia and achieve adequate cycle control. The primary cause of AUB in adolescents is anovulation, caused by the immaturity of the hypothalamic-pituitary-ovarian axis. However, prior to any treatment, pregnancy should be excluded.

Bleeding can usually be controlled with combined oral contraceptive pills (OCPs) taken continuously for several months. OCP's containing 20–30 µg of ethinyl estradiol and a relatively androgenic progestogen such as 0.3 mg of norgestrel or 0.15 mg of levonorgestrel can be used cyclically. If breakthrough bleeding occurs, or heavy menstrual bleeding persists and other causes of AUB have been excluded, the dose can be doubled for a short period of time to two pills per day. Since combined hormonal contraceptives can increase levels of coagulation factors such as factor VIII and von Willebrand factor, OCP's might have an additional effect in

cases of an underlying coagulopathies. If estrogen is contraindicated due to a history of thrombosis, migraine, hypertension etc., progestogens alone can be used. Examples are: oral medroxyprogesterone acetate (MPA), or NETA. Oral MPA 10 mg daily or NETA 5 mg can be given for 10–14 days each month to generate a secretory endometrium that induces a withdrawal bleed 1–7 days after stopping the medication. NETA can be aromatised to ethinyl estradiol [31]. Kuhnz et al [32] reported that this conversion resulted in a dose that was equivalent to taking 4–6 μg of ethinyl estradiol for each 1 mg of NETA ingested. The conversion ratio of NETA to EE has been subsequently estimated to be between 0.2% and 0.33% for different doses [33], Chu et al. [34] concluded that a daily dose of 10–20 mg NETA equates to taking a 20–30 μg ethinyl estradiol COC, Conversion to estrogen and the estrogenic effects are of no relevance when these progestogens are taken in low-dose progestogen-only, or combined oral contraceptive pills [35] but probably explains why high-dose NETA is effective at delaying and regulating menstrual bleeding. There are no similar implications for other progestogens in either low or high doses, since conversion to estrogen does not occur [36–38].

It has been reported in other chapters in this book that dydrogesterone binds the progesterone receptor up to 50% more than progesterone itself. However, dydrogesterone stimulates the progesterone receptor alone. It may therefore be appropriate in patients with a thickened endometrium in whom progesterone only effects are required. However, if there is a thin endometrium, estrogen will also be required to provide hemostasis, in addition to dydrogesterone.

The LNG-IUS or etonogestrel/ethinyl estradiol vaginal ring are other possibilities, but may not be acceptable in adolescents. Clomiphene citrate has occasionally been used in anovulatory adolescents. Clomiphene is a selective estrogen receptor modulator (SERM) which blocks the estrogen receptor in the hypothalamus, thus inhibiting the negative feedback. Therefore, estrogen levels can rise to the level required to induce LH release. The use of clomiphene has been reported as a possible therapy in anovulatory adolescents [39]. During the use of clomiphene citrate in adolescents the chance of conception and the rare possibilities of side-effects (headaches, vision changes, ovarian hyperstimulation, etc.) should be taken into consideration.

6.3 *Perimenopausal Bleeding*

As there is a high incidence of organic disease in perimenopausal women, organic disease must be excluded before progestogen therapy is initiated. As in other age groups, anemia may need to be corrected. Perimenopausal women with AUB may be treated with cyclic progestin therapy, low-dose oral contraceptive pills, the levonorgestrel IUD, or cyclic hormone therapy. Each treatment modality has advantages and disadvantages. The OCP and LNG-IUS provide contraception, in addition to reduction in bleeding volume. Estrogen therapy also provides relief from perimenopausal symptoms, such as hot flashes, night sweats, and vaginal atrophy. The choice

of therapy often is guided by the patient's priorities. Endometrial thickness will also indicate whether estrogen is required, or whether the patient can be managed on progestogen alone. In a study of 120 perimenopausal women, suffering from irregular menstrual cycles, treated by continuous estrogen and cyclic progestin or cyclic progestogen alone [40], 86% of women in the combined treatment group experienced cyclic menstrual bleeding, and reduced vasomotor symptoms. In addition, 76% of the women rated their bleeding as normal in amount and duration.

6.4 *Chronic Abnormal Bleeding*

Many regimens of progestogens have been used, and there are some comparative studies of different regimens. Dydrogesterone has been compared to micronized vaginal progesterone [41]. 69 women with irregular dysfunctional uterine bleeding were randomly assigned to receive oral dydrogesterone or vaginal progesterone. After three months of treatment, endometrial histology and menstrual cycle characteristics were comparable. However, oral dydrogesterone was far more convenient as it did not require the patient to leave her daily activity, and retire to a clean room to insert vaginal tablets or gel.

NETA and MPA are the two most commonly used progestogens. However, it must be borne in mind that NETA has estrogenic activity, but no glucocorticoid activity, whereas MPA has no estrogenic activity, but does have glucocorticoid activity. NETA seems to have a better effect than MPA in controlling irregular vaginal bleeding.

Depot injectable progestogen (medroxyprogesterone acetate 150 mg IM every 3 months) has been used as in contraception. However, depot MPA can lead to amenorrhea in up to 24% of women, suggesting it is a good option for women with increased bleeding. However, the side effects (irregular bleeding, weight gain, and headache etc. often lead to discontinuation of treatment [42].

A combination of dienogest and estradiol valerate (marketed as Qlair) has been shown to reduce menstrual bleeding [43] and has been approved for such use by the United States Food and Drug Administration (FDA). However, this combination has an anovulatory action, therefore is only indicated in women who have no desire to conceive.

It is convention, that if the contraceptive pill is used, it should be administered cyclically. Cyclic administration is classically for 21 days with a 7 day "pill free interval". Menstruation occurs in the 7 pill free days. More recently, oral contraceptives have been introduced with a 24 day regimen and 4 pill free days. The 24/4 regimen gives better cycle control. However, it is not problematic to take the pill continuously for extended periods, thus allowing the endometrium to recover after heavy menstrual bleeding. Additionally, there is a new contraceptive vaginal ring, containing ethinyl estradiol and segestrol as the progestogen. [44] which provides contraception for 1 year. This contraceptive ring can be left for extended periods in order to lessen the number of menstruations per year.

7 LNG-IUS

The LNG-IUS is particularly useful for the treatment of heavy menstrual bleeding in women who desire contraception. The LNG-IUS has been shown to be the most effective treatment in reducing menstrual blood loss compared with other medical therapies for chronic AUB and can reduce menstrual blood loss by more than 80% and even induce hormonal amenorrhea. However, the LNG-IUS takes time to achieve adequate endometrial quiescence. Initially there may be increased bleeding. The LNG-IUS results in a greater increase in hemoglobin and serum ferritin levels after 6 months compared with oral MPA from day 16–26 of the menstrual cycle [45]. Women also reported higher rates of subjective improvement in their bleeding despite the known initial side effect of irregular bleeding after LNG-IUS insertion. The efficacy of the levonorgestrel IUS was evaluated by Vilos et al. [46] in 56 obese perimenopausal women with AUB. The mean age was 42 years and the mean body mass index was greater than 30. At the 48-month follow-up, the satisfaction rate was 75%; amenorrhea and hypomenorrhea were noted with longer use. Hence, The LNG-IUS is an excellent long-term treatment modality for heavy menstrual bleeding when contraception is also required.

8 Endometrial Hyperplasia

Endometrial hyperplasia, whether simple or complex, with or without atypia has malignant potential. Figure 7.2 shows a sonogram of endometrial hyperplasia. If atypia is present, there is a 29% risk of progression to endometrial cancer [47]. However, in simple hyperplasia, the risk can be as low as 1%. In the perimenopausal or post-menopausal woman, hysterectomy is probably the best treatment option. However, in younger women, endometrial hyperplasia can be found in anovulatory cycles, polycystic ovary syndrome, or obesity. If fertility is desired, progestogens are the mainstay of treatment. There is no need for estrogen as the condition is due to excess stimulation with unopposed estrogen. The role of progestogens is to convert the endometrium to a secretory pattern. Once endometrial hyperplasia has been diagnosed, it is essential to repeat the biopsy 3–6 months later to confirm that regression has taken place. However, the median length of progestin treatment required for regression can be up to nine months. Additionally endometrial hyperplasia is closely related to insulin resistance and metabolic disorder. A low body mass index of $<35 \text{ kg/m}^2$ has been reported to be associated with a high resolution rate in patients receiving progestogens [48]. There are case reports which show that if there is no response to progestogens, reversal of hyperplasia could be induced with metformin in addition to progestogens [49].

The main progestogens for treating endometrial hyperplasia are megestrol acetate, medroxyprogesterone 17-acetate [MPA], dydrogesterone and the LNG-IUS. However, there is no consensus on dose, treatment, duration, route of

administration, or randomized controlled trials as to the most effective progestogen [50]. Hence treatment is somewhat empiric, and administered on a trial and error basis. The overall response rate has been reported to be approximately 70%. Moreover, oral progestins are associated with poor compliance and systemic side effects that may limit overall efficacy [51]. Below are some of the advantages and disadvantages of each regimen.

Megestrol has anti-estrogenic and anti-androgenic effects, which may not be acceptable to the patient, or may decrease compliance. Megestrol acetate also has glucocorticoid effects. Symptoms of Cushing's syndrome, steroid diabetes, and adrenal insufficiency, have been reported with the use of megestrol acetate in the medical literature, albeit sporadically [52].

Medroxy progesterone acetate (MPA) however, is an agonist of the progesterone, androgen, and glucocorticoid receptors [53]. Hence there may be side effects of acne and hirsutism in some patients. MPA has glucocorticoid properties, and as a result can cause Cushing's syndrome, steroid diabetes, and adrenal insufficiency. Mesci-Haftac et al. [54] assessed 69 patients with simple hyperplasia, who received MPA. Hyperplasia persisted in 19.7%. Atypia and progression to complex hyperplasia occurred in 3.2% of the patients.

In 1988, Meden-Vrtovec and Hren-Bozic [55] reported on 50 patients with cystic glandular hyperplasia who were treated with dydrogesterone for six cycles in a dose of 20–30 mg. Repeat curettage showed persistence of the hyperplasia in 5 of 18 patients (28%).

Micronized progesterone was introduced in order to provide a bio-identical form of progesterone. Due to metabolism in the liver, it is often administered vaginally, allowing it to by-pass the liver, and have an increased local concentration in the endometrium. Tasci et al. [50] compared sixty premenopausal women with endometrial hyperplasia without atypia in a prospective controlled study. Group I included 30 patients who received lynestrenol in a dose of 15 mg. per day while Group II included 30 patients who received micronised progesterone 200 mg per day for 12 days per cycle for 3 months. After 3 months of treatment no patient in either group showed progression of the hyperplasia. In the lynestrenol group, the rate of resolution was higher than in the micronized progesterone group ($p = 0.045$). Lynestrenol was more effective in inducing resolution in patients more than 45 years ($p = 0.036$). The authors concluded that lynestrenol ensures better endometrial control than micronized progesterone at the above doses in simple hyperplasia without atypia.

The Levonorgestrel Intrauterine device has also been used to treat endometrial hyperplasia. The LNG-IUS has been compared to other progestogens: Dydrogesterone, NETA and MPA. El Behery et al. [56] assessed the results of 138 women aged between 30 and 50 years with AUB and hyperplasia were randomized to receive either LNG-IUS or dydrogesterone for 6 months. The outcome measures were regression of hyperplasia, and side effects or recurrence during the follow-up period. After 6 months of treatment, regression of hyperplasia occurred in 96% of women in the LNG-IUS group versus 80% of women in the dydrogesterone group ($p < 0.001$). Intermenstrual spotting and amenorrhea were more common in the

LNG-IUS group ($p = 0.01$ and 0.0001 , respectively). Patient satisfaction was significantly higher in the LNG-IUS group ($P = 0.0001$). Hysterectomy rates were lower in the LNG-IUS group than in the dydrogesterone group ($p = 0.001$). The recurrence rate was 0% in the LNG-IUD group compared to 12.5% in the dydrogesterone group. Gallos et al. [57] reported similar results.

The LNG-IUS has also been compared to NETA [58]. 129 perimenopausal women with non-atypical endometrial hyperplasia were assessed in a randomized controlled trial. Patients received either the LNG-IUS or NETA for 3 weeks per cycle for 3–6 months. A significantly higher regression rate was noted in the LNG-IUS group than in the NETA group (79.7% vs. 60.7%, RR, 1.31 after 6 months). However, no significant difference was found regarding the median time to regression (3 months). The hysterectomy rate during the follow-up period was significantly higher in the NETA group (57.4% vs. 22%, $p < 0.001$).

In a prospective RCT [59] comprising 90 premenopausal women with a histological diagnosis of simple endometrial hyperplasia without atypia, patients were randomly allocated to 3 groups of 30 patients. One group received MPA, 10 mg. per day. The second group received NETA, 15 mg. per day for 10 days per cycle. The third group had a LNG-IUS inserted. Patients were re-evaluated after 3 months of treatment. Patients with regression and persistence were offered the same medication they were using for another 3 months. Patients in the LNG-IUS group showed the highest resolution rate (66.67%). Patients in the MPA and NETA groups had a resolution rate of 36.66% and 40%, respectively. The patients with a LNG-IUS showed a regression rate of 33.3%, whereas patients receiving MPA and NET showed a regression (and persistence) rate of 60% and 56.67%, respectively. There was a statistically significant difference between the three groups regarding the proportion of patients requiring further treatment for another 3 months ($\chi^2 = 6.501$; $P = 0.0387$) in favour of the LNG-IUS.

9 Other Forms of Treatment

9.1 Receptor Modulators

Receptor modulators have been used in preliminary trials and have shown promising results. The selective estrogen receptor modulator (SERM), ormeloxifene has an anti-estrogenic effect, which retards endometrial maturation. In a randomized study, Ravibabu et al. [60] reported that ormeloxifene decreases blood loss by 90%, and that the reduction was statistically significant ($p < 0.001$). There was also a significant decrease in the mean endometrial thickness ($p < 0.001$) after treatment with ormeloxifene when compared to mean baseline value. There was significant improvement, 84% of patients had relief from dysmenorrhoea ($p < 0.001$), but anti-estrogenic side effects such as hot flashes and vaginal dryness are a cause for concern.

Ormeloxifene has been compared to medroxyprogesterone acetate. The results were similar in terms of mean duration of bleeding, increased hemoglobin concentration and endometrial thickness [61]

Mifepristone (Ru486), is a selective progesterone receptor modulator (SPRM). Mifepristone induces amenorrhea whilst maintaining endogenous estrogen secretion. Amenorrhea is caused by complete binding of the progesterone receptor, causing atrophy of spiral arteries and hence, anovulatory amenorrhea [62]. Another SPRM is ulipristal acetate. Ulipristal was introduced mainly to shrink uterine myomas. However, reports of liver toxicity have precluded its continued use. If SPRMs are used, it must be borne in mind, that there is an effect on the endometrium known as ‘progesterone receptor modulator associated endometrial change (PAEC) [63].

9.2 NSAIDS

A certain amount of relief may be obtained from non steroidal anti-inflammatory drugs (NSAIDs). NSAIDs inhibit the enzyme cyclooxygenase, thereby reducing the raised prostaglandin levels which are found in women with heavy menstrual bleeding. A Cochrane review [64] showed that NSAIDs (mefenamic acid, naproxen, ibuprofen, flurbiprofen, meclofenamic acid, diclofenac, indomethacin, and acetylsalicylic acid) are more effective than placebo in reducing menstrual blood loss by 25–30% in women with regular menstrual cycles [65], but have a limited effect on the reduction of HMB [65] and are less effective than tranexamic acid, danazol, or the levonorgestrel-releasing intrauterine device (LNG-IUS) [66]

9.3 Antifibrinolytic Drugs

Tranexamic acid is a lysine analogue that allows the formation of stable blood clots by preventing fibrin filament breakdown without influencing coagulation in healthy blood vessels. Data from controlled clinical trials indicate reduced bleeding in AUB by 30–55% [67, 68]. However, there are side effects including headache, nausea and vomiting. Tranexamic acid is the only nonhormonal, noncontraceptive agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of HMB. Concerns have been raised about the potential for thromboses during tranexamic acid treatment. However, population-based data do not indicate an increased risk of thromboses [69]. Tranexamic acid is most often used for women in their reproductive years to reduce heavy menstrual bleeding. One potential benefit is that tranexamic acid is only used during menstruation rather than continuously or for the majority of the menstrual cycle.

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