

Endometrial bleeding

The ESHRE Capri Workshop Group^{1,2}

Abnormal bleeding is a significant health problem, especially during adolescence and before menopause when anovulatory cycles are common. Curettage is rarely necessary to investigate or treat menstrual problems in adolescents, and its use should also be minimized in women younger than 40 years. In every age group, medical treatment is the initial choice, but surgical treatment by endometrial destruction or hysterectomy is sometimes required. Benign causes of bleeding include fibroids and possibly adenomyosis, but the indications for treatment in each case depend upon the extent of bleeding, not the extent of the lesion. Breakthrough bleeding (BTB) with combined oral contraceptives commonly leads to discontinuation of the method. As BTB tends to improve with time, in the first 3 months of pill use, unless there are obvious underlying causes, women should be reassured that it will likely settle. BTB is often the reason for discontinuing progestogen-only contraception, and there is a need for effective means of treating unscheduled bleeding. Bleeding occurs in ~3% of post-menopausal women, and the use of hormones increases the likelihood of bleeding by >5-fold. Knowledge of the underlying mechanisms of bleeding is essential to the development of effective treatment.

Keywords: menstruation/endometrial bleeding/heavy menstrual bleeding

Introduction

Heavy menstrual bleeding is a major public health problem, considering that between 30 and 49 years of age, 1 in 20 women each year consults a general practitioner for bleeding (Garside *et al.*, 2004). Moreover, 20% of women by the age of 60 have a hysterectomy, mainly for heavy bleeding, despite the fact that 40% have a normal uterus on histological examination (Maresh *et al.*, 2002). Menstrual disorders interfere significantly with the quality of life

in otherwise healthy women. In the UK, 3.5 million work-days are lost per year and annual treatment costs for excess bleeding are >65 million pounds, reflecting the high cost of hysterectomy (Weeks *et al.*, 2000). In 2002, over 13 000 surgical procedures were performed in UK for complaints of heavy menstrual bleeding (Reid and Mukri, 2005). Troublesome bleeding is most frequent near the beginning and end of the menstrual life when anovulatory cycles are most common. Whenever bleeding occurs, judgment is needed to determine whether investigation is required to rule out benign and malignant causes. This review will provide a background on the mechanisms of normal endometrial bleeding as a key to the knowledgeable management of abnormal bleeding. Clinical management is discussed for bleeding occurring during the early and late reproductive life, during contraception and in the menopause.

How did the menstrual cycle evolve

Periodic vaginal bleeding from the uterus is characteristic of old world primates and man and a small number of other mammals, e.g. the elephant shrew and certain species of bat (Mac Donald, 1971). The bleeding results from shedding of the endometrial lining of the uterus at the end of a sterile ovarian cycle. Why these species have evolved this mechanism for re-starting a new cycle is not known, although we know that endometrial shedding is associated with the presence of uterine spiral arterioles. It may be that, in those species, a degree of decidualization of the endometrium occurs in the luteal phase, even in the absence of an embryo and that endometrial shedding characteristic of menstruation can only occur from decidual tissue (Finn, 1986). As the average menstrual cycle in women is 28 days, it is a popular

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belief that its length was timed to the phases of the moon. It is perhaps more plausible that the rather long ovarian cycle, when compared with many animals, reflects the time necessary to repair and prepare the endometrium for implantation (Baird, 1988).

Attitudes to menstruation

In every society, menstruation is surrounded by a wealth of customs and traditions which reflect the varied reactions of individual women to a repeated monthly event over which they have little control (Drife, 1998). The onset of menses at puberty is a sign of the transition from girlhood to womanhood. In some cultures, the menarche is a public event with festivities celebrating the onset of fertility. In others, the menstruating woman is considered dirty, dangerous and poisonous. These contrasting responses represent the ambivalent attitudes of society and individual women to menstruation. Even in the 21st century, many women feel socially excluded during menses.

Pattern of menstrual cycles

The length of the menstrual cycle is somewhat variable at the beginning and end of reproductive life, due to variability in ovulation intervals immediately after menarche and before menopause (Treloar *et al.*, 1967). However, it is remarkably constant for an individual woman, although there is a slight but significant fall in length with age. This is due to a shortening of the follicular phase of the cycle rather than any change in the length of the luteal phase (Sherman *et al.*, 1979).

Although many women and health professionals think that cyclical menstrual bleeding is natural and must be ‘...good for you because it gets rid of bad blood.’, there is no scientific or medical basis for any perceived health benefits of menstrual periods.

Rather, repeated menstruation causes impressive inconvenience and morbidity (Royal College of Obstetricians and Gynaecologists, 1998). Until modern times, menstrual cycles were the exception rather than the norm because most women were amenorrheic during pregnancy and lactation (Short, 1976). Earlier menarche and a striking decline in fertility rates in most countries of the developed world have been associated with a rise to >400 menstrual cycles in the lifetime of the average woman. Although the use of contraception is prevalent, the methods of contraception in widest use have perpetuated menstrual cycles (condoms, copper and inert intrauterine devices and sterilization). Even the combined oral contraceptive (COC) pill is prescribed to be taken for 21 out of 28 days and resulting in monthly periodic bleeding.

Attitudes to amenorrhea

It has been assumed by many health professionals that women would prefer to menstruate at regular monthly intervals. This view was supported by the results of large surveys of women’s attitudes conducted by WHO and others in the 1970s and 1980s, in which the proportion of women who were prepared to use a method of contraception which caused amenorrhea ranged from 47% in UK to <10% in Pakistan (World Health Organisation Task Force on Psychosocial Research in Family Planning, 1981). Women thought that amenorrhea would be harmful to

Table I. Clients’ and providers’ attitude toward amenorrhea induced by contraception (Glasier *et al.*, 2003)

	Centers						
	ED	CT			HK	SH	NG
		B	W	C			
Women who like having periods (%)	26	75	35	42	50	33	81
Providers who perceive that bleeding is important for women (%)	18	47	13	18	65	82	74

ED, Edinburgh; CT, Cape Town; HK, Hong Kong; SH, Shanghai; NG, Nigeria; B, black; W, white; C, colored.

their health. Moreover, they were concerned that in the absence of periods they would be unsure whether their contraceptive method had failed and they might be pregnant.

Amenorrhea has been considered an undesirable side effect of hormonal contraception, although methods such as depot medroxyprogesterone acetate (DMPA), which frequently result in amenorrhea, are popular in many developing countries. In developed countries, DMPA use is largely confined to those women who suffer from troublesome symptoms such as dysmenorrhea and heavy menstrual bleeding.

A recent study by den Tonkelaar and Oddens (1999) indicates that attitudes in Europe may be changing. In this study, the wish for amenorrhea was positively related to age, probably because women reaching their 40s look forward to relief from the burden of monthly bleeding at the menopause. Similar attitudes were reported in women in developing countries such as Nigeria, South Africa and China (Table I) (Glasier *et al.*, 2003). Interestingly, in some countries, the providers’ perceptions of the women’s attitudes were much more conservative than the attitudes of the women themselves. Since pharmacological methods to manipulate the menstrual cycles safely now exist (Andrist *et al.*, 2004), it may be time to give women the choice of if and when to menstruate (Thomas and Ellertson, 2000).

Mechanisms of menstruation

Menstruation is the cyclical shedding of the endometrium, which is a manifestation of cyclical ovarian function in the absence of pregnancy. Shedding of the superficial two-thirds of the endometrium occurs in response to a fall in estrogen and progesterone at the time of luteal regression. During normal menstruation, most of the tissue is shed in the first 1 or 2 days. Bleeding continues, however, for several days until the damaged epithelial lining is repaired by regeneration and proliferation (Noyes *et al.*, 1950).

Endocrine control

Steroids interact with the uterus via their specific receptors localized in the cell nucleus in the glands and stroma of the endometrium, myometrium and blood vessels (Jabbour *et al.*, 2006). Estrogen secretion in the follicular phase increases the expression of estrogen receptors (ER), progesterone receptors (PR) and probably androgen receptors; in contrast, ER and PR are down-regulated in the epithelium by progesterone. Notable is the

persistence of PR in the stromal compartment in the secretory phase (progesterone dominance). In the first half of the cycle, unopposed estrogen produces a proliferative endometrium. The transformation to a secretory histology under the influence of progesterone is accompanied by pre-decidual changes which prepare the endometrium for implantation of the embryo.

While uterine bleeding can occur in response to a fall in estrogen alone, normal menstruation occurs after luteal regression from an endometrium which has been exposed to both progesterone and estrogen. The classical studies of Markee in the rhesus monkey established that the bleeding induced by withdrawal of progesterone was preceded by changes in the endometrial vessels (Markee, 1940). Initial shrinkage of the stroma, with coiling of the spiral arterioles and vascular stasis, was followed by vasodilatation and perivascular bleeding. Some 24 h later, there was intense vasoconstriction, hypoxia, tissue necrosis and bleeding. These observations led Markee to propose that vasoactive substances must be involved. It soon became apparent that prostaglandins (PGs) had many of the properties which made them very likely candidates to be involved in the vascular and myometrial changes which occur at menstruation (Baird *et al.*, 1996).

Paracrine and Intracrine factors

Recent research has defined better the complex molecular and cellular events which occur following withdrawal of progesterone. Key changes occur in the perivascular area involving stroma and endothelium as well as cells of the immune system (Critchley *et al.*, 2001; Brenner *et al.*, 2002). Some of the local mediators implicated include chemokines: the alpha chemokine CXCL8 [or neutrophil chemotactic factor, interleukin (CIL)-8] and the beta chemokine CCL-2 [or monocyte chemotactic peptide-1(MCP-1)], as well as the inducible enzymes responsible for synthesis of PGs [cyclo-oxygenase (COX)-2] and their degradation (prostaglandin dehydrogenase (Fig. 1).

After progesterone withdrawal, there is an increase in PG synthesis and a decrease in metabolism (Baird *et al.*, 1996). 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 (Colditz, 1990; Critchley *et al.*, 2001).

The early events following withdrawal of progesterone are probably reversible if progesterone levels are restored (Slayden and Brenner, 1999). After 36 h, however, a cascade of irreversible changes in the structure and viability of the endometrium is induced by the release of lytic mediators including IL-1, matrix metalloproteinases (MMP)-1 and MMP-7 (Salamonsen *et al.*, 2002).

Hemostasis

A curious feature of the blood vessels at menstruation is that platelet aggregation and fibrin deposition are modest when compared with what is found following vessel damage elsewhere in the body (Sixma *et al.*, 1980). This poor response of the coagulation system suggests that some local anticoagulant is released and accounts for the fact that menstrual bleeding is prolonged over 3–5 days and is not usually followed by scarring. The uterus is a rich source of PGs including PGI₂, and the uterine fluid contains high fibrinolytic activity and fibrin degradation products, findings which suggest that active fibrinolysis has taken place.

Regeneration and proliferation

Following menstruation, the endometrium undergoes repair (Tabibzadeh, 1996; Salamonsen, 2003). Under the influence of estradiol (E₂), regeneration of all cell types, including epithelial,

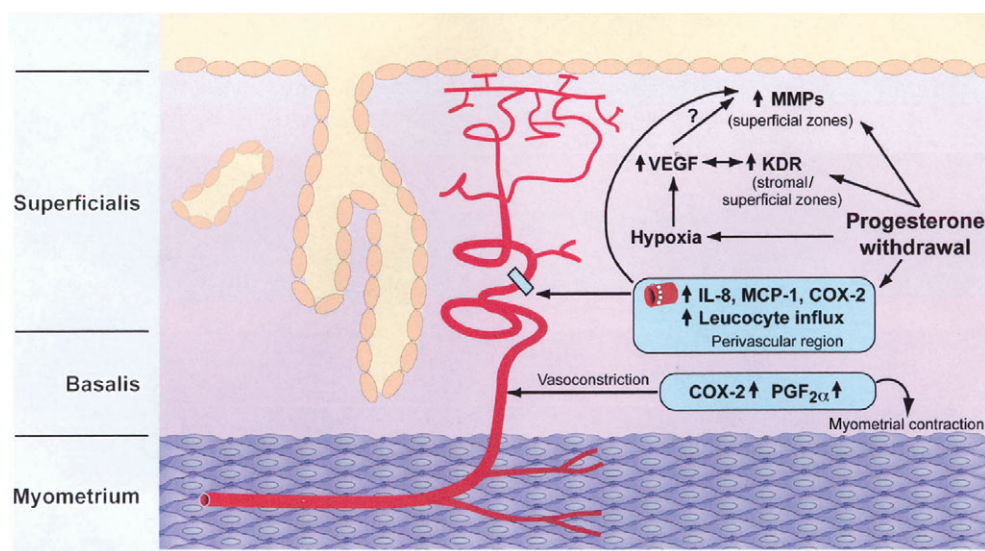


Figure 1. Molecular and cellular events occurring after progesterone withdrawal (Critchley *et al.*, 2001). Coincident events of progesterone withdrawal and hypoxia. Progesterone withdrawal results in an up-regulation of inflammatory mediators, production of MMPs, a leucocyte influx and expression of stromal KDR in the upper endometrial zones. There is coincident hypoxia and an up-regulation of VEGF. VEGF binds to its type 2 receptor, KDR, and there is a paracrine/autocrine action on the up-regulation of MMP production in the same endometrial upper zone stromal cells. Menstrual sloughing takes place from the superficial regions of the endometrium. KDR, kinase insert domain-containing receptor or VEGF receptor 2; PGF_{2α}, prostaglandin F_{2α}.

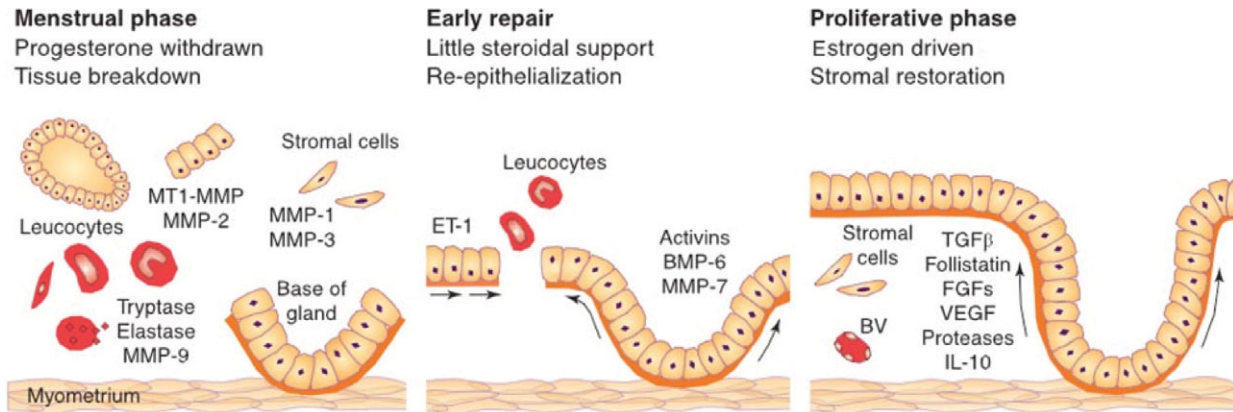


Figure 2. Breakdown and restoration in the endometrium. Tissue is shed as a result of the action of MMP. Re-epithelialization is very rapid and occurs from the open mouths of the glands and from the unshed portions of the luminal epithelium. Leucocyte products and a variety of other factors derived from the epithelium itself are postulated to play a role in re-epithelialization. Subsequent restoration of the underlying stroma includes proliferation of cells associated with blood vessels and endometrial stromal cells, along with the laying down of the extracellular matrix. These events are postulated to occur under the influence of increasing estrogen concentrations and are probably locally regulated by a number of growth factors and other regulatory factors (Salamonsen, 2003). MT1, membrane type 1; ET-1, endothelin 1; BMP-6, bone morphogenetic protein 6; BV, blood vessel; FGFs, fibroblast growth factors.

endothelial and stromal types, occurs very rapidly. The exposed surface is rapidly covered with fibronectin and leucocytes, which are removed as the epithelium is regenerated (Fig. 2). Full coverage and repair are not complete until day 6. A host of local growth factors are involved in this burst of regeneration, including epidermal growth factor, transforming growth factor α (TGF α), endothelins and vascular endothelial growth factor (VEGF). These factors are also involved in the massive angiogenesis which reconstitutes the unique vessels of the endometrium. It has been suggested that the rather long follicular phase characteristic of the primate ovarian cycle has evolved to allow the necessary time for the repair and regeneration of the endometrium (Baird, 1988).

Menstruation involves repeated cycles of tissue destruction, regeneration and proliferation unrivalled by any other tissue in the adult body. Because of its unique importance for reproduction, the endometrium has evolved a highly specialized mechanism of repair and regeneration. Many of the events and molecules are those involved in the inflammatory response to injury. Perhaps the endometrium—a tissue specialized for receiving the embryo—is discarded every month to avoid the sequelae which normally follow tissue damage.

Bleeding in adolescence

The successful completion of puberty is a pre-requisite for reproduction. The onset of puberty is initiated by increases in the amplitude and frequency of pulsatile LH secretion, leading to a 100-fold increase in mean serum LH concentrations (Apter *et al.*, 1993). FSH also increases, although to a lesser extent, and the gonads produce sufficient sex steroids for menarche to occur at the mean age of 12–13 years.

During the first 2 years, the menstrual cycle is often quite irregular. If menstrual cycle irregularities persist for >2 years after menarche, there is a high likelihood of adult menstrual irregularities and infertility (Apter and Vihko, 1990). The majority of bleeding disturbances in adolescence likely reflects the exposure of the endometrium to uncoordinated circulating estrogen and

Table II. Percentage of ovulatory cycles in relation to menarche

Years since menarche	Number of cycles	Ovulatory cycles ^a (%)
0.0–0.9	34	15
2.0–2.9	41	41
5.0–5.9	20	74
8.0–12	33	85
12–18	28	96

^aOvulatory cycle, serum progesterone > 6.4 nmol/l (>2.0 ng/ml) in specimens drawn on days 20–23 and/or later in the cycle (Apter, 1997).

progesterone concentrations as a consequence of irregular or anovulatory cycles. The menstrual cycle is not yet mature, and anovulation occurs frequently (Table II). The exposure to unopposed estrogens leads to proliferation of the endometrium and eventually to oligomenorrhea or breakthrough bleeding (BTB). The bleeding is irregular and mostly rather painless. Stress, heavy exercise and low caloric intake predispose first to anovulation with lack of luteal function and, at more extreme levels, to low estrogen secretion and amenorrhea.

Obesity or endocrinopathies such as hyperprolactinemia, thyroid disturbances or hyperandrogenism are other possible causes and should be treated specifically. Evaluation of an adolescent’s bleeding requires a thorough assessment to rule out other causes such as pregnancy, coagulation disorders and local anatomical lesions.

Endocrine treatment is usually indicated in cases of excessive menstrual bleeding. Curettage can be avoided in most cases. Moderate problematic bleeding is treated with cyclic progestogens (as anovulation likely) and iron supplementation. Acute bleeding is stopped with estrogen treatment to which progestogens are sequentially added. Severe hemorrhage requires hospitalization and transfusion to restore hemodynamic balance. As there is a high risk of repeated heavy bleeding, cyclic progestogen treatment should continue for at least 3 months. Oral contraceptives can also be used and may be continued for as long as necessary (Table III). A heritable coagulopathy must be excluded.

Bleeding in the Fertile Age

Heavy menstrual bleeding has been defined as an objective measured blood loss in excess of 80 ml of blood per menstrual cycle (Warner *et al.*, 2004a, b) and in young women may be associated with different conditions (Table IV).

Abnormal clotting mechanisms, such as Von Willebrand's disease, may contribute to excessive bleeding, but these represent a small proportion of women presenting with heavy blood loss (Munro *et al.*, 2005).

In addition, benign disorders such as fibroids and endometrial polyps may present with heavy menstrual bleeding (Fig. 3). Prior to the menopause, anovulatory cycles increase in frequency (Landgren *et al.*, 2004) and menstruation tends to be abnormal with prolonged spotting and/or heavy bleeding (Burger *et al.*, 2005). Women with irregular cycles experience frequent episodes of mental stress as they wonder whether bleeding will occur, and women suffering from heavy monthly bleeding are often anemic and in poor health and their quality of life is greatly impaired.

Mechanisms of excess bleeding

The underlying mechanisms may involve disturbances in the regulation, expression and signalling processes of local mediators

Table III. Management of problematic menstrual bleeding in teenagers

Hemoglobin > 12 gm/100 ml
Reassurance
Menstrual calendar
Iron supplements
Periodic re-evaluation
Hemoglobin 10–12 gm/100 ml
Reassurance and explanation
Menstrual calendar
Iron supplements
Cyclic progestin therapy or oral contraceptives
Re-evaluation in 6 months
Hemoglobin < 10 gm/100 ml
No active bleeding
Explanation
Iron supplements
Hormonal therapy
Reevaluation in 6 months
Acute hemorrhage
Transfusion
Fluid replacement therapy
Hormonal hemostasis (OC × 4; estradiol valerate 2–4 mg per day for 7–10 days; intravenous conjugated estrogen)
Progestogen therapy medroxyprogesterone acetate 10 mg per day for 7–10 days
Dilatation and Curettage when hormonal hemostasis fails
Hormonal follow-up treatment
Continue with cyclic progestogen for 10 days per month, cycle days 15–24
Oral contraceptives

Table IV. Causes of heavy menstrual bleeding

Local uterine causes	Iatrogenic causes	Systemic causes	Idiopathic causes
Leiomyoma	Anticoagulants	Coagulation disorders	Altered synthesis of uterine vasodilatory prostanoids
Polyp	Copper intrauterine device	Hypothyroidism	Reduced endothelin expression
Infection		Chronic liver disease	Increased fibrinolysis
Adenomyosis			Perturbed endometrial regeneration
Pelvic antero-ventral malformation			Overproduction of nitrogen oxide

within the endometrium, although endometrial or myometrial histology and sex steroid receptor concentrations do not differ in women with normal and heavy blood loss (Rees *et al.*, 1984; Critchley *et al.*, 1994). Factors involved with vasculogenesis, such as increased endometrial endothelial cell proliferation, has been reported in women with heavy menstruation. Furthermore, the proliferation and differentiation pattern of the vascular smooth muscle cells around spiral arterioles of the endometrium of women with heavy bleeding is reduced when compared with that of women with normal menstruation. Data such as these indicate likelihood of an aberration in the composition and structural integrity of blood vessels in women with heavy menstrual bleeding (Rogers and Abberton, 2003; Jabbour *et al.*, 2006). Altered synthesis and production of uterine vasodilatory prostanoids may cause heavy menstruation, for example, endometrial PGE₂ synthesis, PGE binding sites, prostacyclin concentrations and COX activity all correlate with menstrual blood loss. COX inhibitors are commonly prescribed to reduce menstrual blood loss (reviewed in Jabbour *et al.*, 2006). Abnormalities of endothelial factors in the endometrium of women with heavy menstrual bleeding have been recently reported (Malik *et al.*, 2006). VEGF-A was reduced in the menstruated endometrium of these women, indicating an abnormality in factors involved with endothelial cell function. Endothelin expression is reduced in women with heavy menstrual blood loss, with the potential consequence that a fragile endometrium may be predisposed to bleed through alteration in the constrictive potential of blood vessels (Salamonsen *et al.*, 1999; Jabbour *et al.*, 2006). Expression of endometrial-bleeding-associated factor (also known as LEFTY-A) is increased in the endometrium of women with abnormal endometrial bleeding. These data indicate the complexity and diversity of some of the local factors that may be dysregulated within the endometrial environment in women complaining of abnormal menstrual bleeding.

Medical treatment of heavy menstrual bleeding

Pharmacological agents used for the treatment of menstrual complaints include non-hormonal [non-steroidal anti-inflammatory drugs (NSAIDs) and antifibrinolytics] and hormonal [COEs and progestogens, the levonorgestrel intrauterine system (LNG-IUS), danazol and gonadotrophin-releasing hormone (GnRH) analogs]. NSAIDs reduce bleeding more than placebo, but are less effective than either tranexamic acid or danazol (Lethaby *et al.*, 2002). The non-hormonal agents, mefenamic acid and tranexamic acid, are appropriate as initial treatments for troublesome bleeding, but long-term therapy will usually be more effective with the LNG-releasing IUS, COCs or long-acting progestogens (Showstack *et al.*, 2006). Danazol and GnRH analogs reduce menstrual blood loss, but involve costs and side

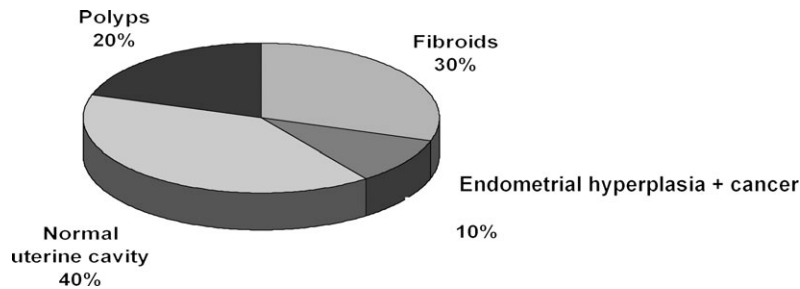


Figure 3. Conditions associated with abnormal uterine bleeding in women between aged 30 and 50.

effects that limit their role to treatment of anemia prior to operations for excessive menstrual bleeding (Roy and Bhattacharya, 2004).

Surgical treatment of heavy menstrual bleeding

A high proportion of women remain unsatisfied with medical treatment: in eight trials, 58% of women randomized to medical treatment had received surgery by 2 years (Marjoribanks *et al.*, 2006). Whether the surgery is endometrial destruction or hysterectomy, quality of life is similar at 1 year. Although with hysterectomy, operating time and recovery period are longer and there are higher rates of post-operative complications, amenorrhea is universal and there are fewer follow-up procedures (Lethaby *et al.*, 2000). Endometrial ablation techniques continue to improve, however, and the new methods are technically easier than hysteroscopic methods; uterine perforation is an uncommon risk that requires hysteroscopy for diagnosis (Lethaby *et al.*, 2005). The risk of unwanted conceptions is another limitation of the method (Gervaise *et al.*, 2005). In the last 15 years, at least in Europe, hysterectomy has become a less-frequent option (Reid and Mukri, 2005); nevertheless, the necessary reliance on surgical treatment underlines that better knowledge of the mechanisms involved in uterine bleeding is needed to improve medical treatment and minimize the resort to surgery.

Unscheduled bleeding on combined oral contraception

The use of COC is generally associated with highly acceptable bleeding patterns, with predictable intervals and reduced pain and volume of bleeding. Nevertheless, problems with unscheduled bleeding are a common clinical problem. Intermenstrual bleeding (IMB) is common regardless of their contraceptive method. In a postal questionnaire survey of 2438 UK women, over the course of 1 year self-reported cumulative incidence of IMB was 17% [95% confidence interval (CI) 14–19] (Shapley *et al.*, 2004). In an analysis of almost 300 000 general practitioner consultations in Australia, 1.2% of consultations were because of symptoms suggestive of a sexually transmitted infection, and 9% of these (0.3% of all consultations) were for IMB (Freedman *et al.*, 2006).

When IMB occurs during contraceptive use, it is traditionally called BTB. In a 1992 review of the literature that had been published in the late 1980s, BTB occurred in up to 12.2% of women who had been using the COC pill for >6 months (Rosenberg and Long, 1992). In a 1997 study of 1657 US women initiating or re-starting COCs, 15% discontinued within the first 2 months

of use a total of 28% had discontinued by 6 months. Almost half of the discontinuations (46%) were because of side effects—most commonly bleeding irregularities (12%) (Rosenberg and Waugh, 1998).

Breakthrough bleeding during the use of COC is associated with follicular development, and estrogen levels are in the mid-follicular range. In a retrospective analysis of data from seven prospective clinical studies with five different combined oral contraceptive preparations, 35% of women with large ovarian follicles reported IMB and women with BTB had significantly higher E₂ concentrations than those without (Endrikat *et al.*, 2003).

The likelihood of follicular development occurring during the use of the combined pill depends on the degree of suppression of endogenous ovarian activity. This in turn is certainly related to the amount of ethinylestradiol in the pill (and the duration of exposure to exogenous estrogen) and may be related to the type and dose of progestogen. In a randomized controlled trial comparing two oral contraceptive formulations containing either 30 or 20 µg ethinylestradiol, BTB was significantly more likely with the lower dose pill (Akerlund *et al.*, 1993). Pill brands containing 23 days of active tablets or brands which include a few days of estrogen alone during the pill-free interval are associated with a greater degree of ovarian suppression and less likelihood of follicle growth. They should be associated with less BTB, but most comparisons with other pill types have not compared like with like (the type and dose of progestogen or the phasic nature of the pill vary) (Killick *et al.*, 1998; Endrikat *et al.*, 2001a). In a comparison of two pills, both containing 20 µg ethinylestradiol, with either 100 µg levonorgestrel or 500 µg norethisterone, BTB appeared to be significantly less in the LNG-containing pill (Endrikat *et al.*, 2001b).

The commonest cause of BTB is almost certainly a result of missing pills. In a prospective biomedical study in which two pills were deliberately omitted (on day 6/7 or 11/12) in 10 out of 12 cycles, missed pills were followed by an episode of BTB (Endrikat *et al.*, 2004). Reassuringly, the suppression of ovulation and therefore the effect on efficacy was unaffected. Other causes of BTB during the use of COCs include the use of phasic pills, smoking, drug interactions, vegetarian diet and Chlamydia infection (Thorneycroft, 1999).

Since BTB both worries the woman experiencing it and commonly leads to discontinuation of the contraceptive pill, it should be taken seriously and investigated appropriately. However, BTB tends to improve with time, and, unless there are obvious underlying causes, women should be warned to expect it in the first 3 months of pill use and reassured that it will likely

settle (Edelman *et al.*, 2006). If it does not improve, a careful history should be taken, including questions about missed pills, smoking and use of other drugs including over-the-counter preparations, and an examination done to exclude cervical conditions (ectropion, polyp and malignancy). Testing for Chlamydia infection should be undertaken before trying a pill with a different dose of estrogen or type or dose of progestogen, continuous administration of the pill (Edelman *et al.*, 2006) or a different route of administration (Westhoff *et al.*, 2005).

Bleeding from progestogen only contraception

Over 20 million women world wide use a method of contraception containing a progestogen as the sole active component. The most widely used progestogen-only contraceptive (POC) method is DMPA, followed by the Norplant subcutaneous implant system. These two methods, together with a growing number of less widely used progestogen-only methods, are highly effective in preventing pregnancies; they are also considered by providers and many women to be very convenient because of their long duration of action.

Despite their advantages, POCs are considered less than ideal by many women because the methods disrupt their normal menstrual bleeding pattern. This side effect is the primary reason that women give for discontinuing the use of these methods and accounts for 40–70% of terminations from clinical trials (d'Arcangues *et al.*, 1992; Datey *et al.*, 1995). At 1 year of use, <10% of women using DMPA and only 25% of Norplant users experience regular monthly bleeding, whereas others report a variety of patterns ranging from infrequent bleeding and amenorrhea to irregular, frequent or prolonged bleeding. whereas DMPA users report increasing periods of amenorrhea with continued use, women who rely on Norplant experience more regular bleeding after the first 12 months of use (Khanna, 1999).

Irregular bleeding patterns classified as BTB differ according to the type of progestogen-only method (Newton *et al.*, 1994; Fan and Sujuan, 1996; Suvisaari and Lahteenmaki, 1996; Fraser *et al.*, 1998). Individual women respond differently to the use of POCs, and there seem to be great variations in the tolerance that women have for bleeding disturbances (Said *et al.*, 1987). Break-through bleeding resulting from the use of POCs is unlike menstruation. It starts and stops irregularly and unpredictably, coming from an endometrium that shows none of the cyclical changes associated with menstruation. The endometrium of women using POCs displays aberrant angiogenesis with abnormal, enlarged, thin-walled fragile blood vessels, inflammation and focal hemorrhage (Hickey *et al.*, 2006a). The pathophysiology of progestogen-induced BTB is not yet fully understood (Hickey and Fraser, 2000a).

A variety of treatments have been used by service providers to control or prevent these bleeding irregularities, but uncertainties remain about the benefits and risks of individual treatments, as few have been adequately tested (Fraser, 1983; Nutley and Dunson, 1997). The most extensively studied intervention has been estrogen for treatment or prevention of irregular bleeding. A variety of formulations have been tested in studies of women using DMPA or Norplant. Ethinylestradiol appears to be somewhat effective, whereas none of the estrogenic regimens tested altered the frequency of bleeding episodes or produced mid- or long-term

effects (d'Arcangues, 2000). Women receiving estrogen-based therapies were more likely to experience side effects related to treatment when compared with women receiving placebo.

A single randomized trial examined the efficacy of a selective ES modulator, tamoxifen, on bleeding irregularities experienced by women using Norplant (Abdel-Aleem *et al.*, 2005). Women receiving tamoxifen reported improved bleeding patterns, were less likely to be dissatisfied with their treatment regimen and were no more likely to report side effects.

Additional clinical testing is needed on the value of NSAIDs, low-dose anti-progestogens and selective ES modulators. Further research is also needed on the mechanisms of progestogen-induced BTB, on women's perceptions of bleeding and to determine whether treatments for BTB can reduce discontinuation rates (Smith, 2000).

Bleeding with benign uterine pathology

Bleeding with fibroids

Uterine fibroids (leiomyomas) are clinically apparent in ~25% of women, and after careful pathological examination of surgical specimens, the prevalence may substantially increase. Heavy menstrual bleeding is frequently reported by women with fibroids and may be sufficient to cause iron-deficiency anemia, loss of productivity and social embarrassment (Stewart, 2001). The extent of bleeding and other symptoms play a major role in whether a patient seeks treatment and in what diagnostic test and treatments are performed. There is evidence that women do not change substantially how they report bleeding just because they have an incidental diagnosis of fibroids (Wegienka *et al.*, 2004).

It is an old clinical tenet that fibroids cause heavy bleeding especially if they are submucosal and distort the uterine cavity (Table V). This is due to the high vascularization of the pseudo-capsule and to the large and fragile vascular lacunae present on the surface of submucous fibroids (Hickey and Fraser, 2000b). Owing to the intracavitary position, bleeding from these large calibre vessels during menstruation cannot be stopped promptly by myometrial contractions. In a Scottish study, objectively determined menstrual blood loss correlated with neither fibroid size nor location. All the women with submucosal tumors, however, had a heavy blood loss of >80 ml (Sulaiman *et al.*, 2004). The pathogenic role of submucous tumors is supported also by their high prevalence in women with heavy bleeding (Vercellini *et al.*, 1997), and by the successful follow-up results observed after hysteroscopic resection, with dramatic reductions in menstrual blood loss and correction of iron-deficiency anemia (Vercellini *et al.*, 1999). The relationship between intramural and subserosal fibroids and heavy menstrual blood loss is less clear. Whether uterine fibroids that do not impinge on the uterine cavity cause bleeding has been assessed in the Seveso Women's Health Study (Marino *et al.*, 2004). After adjustment for covariates, the presence of an intramural or subserosal fibroid was not significantly related to the length of menstrual cycle, flow length or heaviness of flow. The number, volume, location (subserosal or intramural) and axial position (anterior or posterior) of fibroids also were not related to menstrual cycle characteristics. Findings are not consistent, however, as data from the Environmental Health Sciences Uterine Fibroid Study demonstrated that intramural and subserosal

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Table V. Characteristics of bleeding by leiomyoma status (Wegienka *et al.*, 2003)

Pad/tampon total Mean (SD)	Prevalence		Length of menses (days) Mean (SD)
	<i>n</i>	%	
All women			
Number of leiomyomata 6.1 (3.8)	314	28	4.1 (1.3)
Any leiomyomata 7.5 (4.9)	596	46	4.4 (1.6)
Largest ≤ 5 cm 7.0 (4.2)	486	44	4.3 (1.6)
Largest > 5 cm 10.7 (7.3)	69	56	4.5 (1.7)
Women with leiomyomata at a single location			
Diffuse only 7.4 (4.2)	108	41	4.3 (1.2)
Non-submucosal only			
Largest ≤ 5 cm 6.5 (3.9)	161	38	4.3 (1.6)
Largest > 5 cm 11.1 (4.8)	21	52	4.3 (1.7)
Submucosal only			
Largest ≤ 5 cm 6.0 (2.3)	25	48	4.4 (1.1)
Largest > 5 cm 6.3 (1.1)	4	67	4.5 (1.0)

fibroids were associated with heavy bleeding to the same extent as submucosal fibroids. In this study, even small fibroids (<2 cm) were associated with increased risk of heavy bleeding, and the risk increased with size (Wegienka *et al.*, 2003).

The myometrial microvasculature is altered in the myomatous uterus, as perfusion increases in the vascular plexus around a fibroid. Alterations in the vascular ultrastructure of myometrial vessels in the presence of leiomyomas have been observed, and dysregulation of angiogenic and other regulatory growth hormones associated with increase in lesion size has been hypothesized (Hickey and Fraser, 2000b). All these factors may contribute to the development of unacceptable heavy menstrual bleeding.

Bleeding with adenomyosis

Adenomyosis is a controversial diagnosis, and there is uncertainty about whether it is associated with excess bleeding. Adenomyosis occurs when the normal boundary between the endometrial basal layer and the myometrium is disrupted and endometrial glands are found in the myometrium. These ectopic intramyometrial glands cause adjacent myometrial hypertrophy and hyperplasia (Vercellini *et al.*, 1993). What triggers this process is unclear.

Islands of adenomyosis may be scattered throughout the uterine musculature, giving origin to the diffuse form of the disease, or less frequently, the endometrial glands are localized in a focal form, the so-called adenomyoma. The ectopic mucosa resembles non-secretory basal endometrium, and a direct connection between the basal portion of the endometrium and the heterotopic foci has been demonstrated. The posterior myometrial wall is usually involved to a greater extent than other sections of the uterus (Ferenczy, 1998). Zaloudek and Norris (1987) indicate that adenomyosis should be diagnosed when the distance

between the lower border of the endometrium and the affected myometrial area is over one-half of a low-power field (~2.5 mm). According to the available evidence, depth of penetration and degree of spread have a major impact on symptoms associated with adenomyosis.

Controversial findings have been reported on the relationship between adenomyosis, heavy bleeding, dysmenorrhea and pelvic pain. Most of these inconsistencies are at least partly attributable to different diagnostic criteria (Parazzini *et al.*, 1997). Several hypotheses have been suggested to explain heavy menstrual flows associated with adenomyosis, including increased endometrial surface, altered PGE/PGF2α balance and hampered myometrial contractility (Vercellini *et al.*, 1993). Moreover, blood vessels appear to be randomly scattered throughout the adenomyotic uterus and endo-myometrial vascularization is increased. Vessels in the ectopic adenomyotic endometrium do not seem to arise from the endometrial vasculature, but may develop *de novo* within the myometrium (Hickey and Fraser, 2000b).

Post-menopausal bleeding

Bleeding occurs in <5% of post-menopausal women who do not use hormones. The use of estrogen or estrogen combined with progestogen therapy increases the likelihood of irregular bleeding associated with a distinct pattern of MMPs and tissue inhibitor production, which is different from that seen in contraceptive-related BTB (Hickey *et al.*, 2006b). The clinical symptom is distressing, as bleeding is also associated with endometrial cancer, which, although rare, must be ruled out. The key to management is knowledge of the relative frequency of benign bleeding, endometrial hyperplasia and endometrial cancer.

Frequency of bleeding

Among 8102 placebo patients in the Women's Health Initiative Estrogen-Progestogen trial (WHI-EP), 13.6% reported bleeding over 5.6 years, or 2.4% per year (95% CI 2.3, 2.6) (Barnabei *et al.*, 2005). Among 125 placebo patients in a raloxifene trial, four (3.2%) reported bleeding over 5 years, or 0.6% per annum (95% CI 0.0, 3.7) (Jolly *et al.*, 2003). The majority of bleeding is short-term spotting, which may not require endometrial assessment (Barnabei *et al.*, 2005). For example, only 5.7% of the WHI-EP patients required endometrial assessment, or 1.0% per year (95% CI 0.9, 1.1). In the Post-menopausal Estrogen/Progestin Interventions (PEPI) trial, 11 placebo group patients required additional endometrial assessment procedures among 119 during 3 years (3.1% per year; 95% CI 0.7, 6.7) (PEPI Trial Writing Group, 1996). Thus, <5% of post-menopausal women under surveillance report bleeding; in many cases, this is no more than spotting which does not recur and may not be clinically important.

Estrogen and estrogen-progestogen increase the likelihood of bleeding. In the estrogen-only group of the PEPI trial, 100 of 119 women receiving 0.625 mg of conjugated equine estrogens (CEE) required additional endometrial assessment procedures (28% per year; 95% CI 19, 38), a 9-fold increase over the rate in the placebo group ($P < 0.001$) (PEPI Trial Writing Group, 1996). With the use of estrogen-progestogen, spotting as well as light, moderate and heavy bleeding were all increased in the WHI-EP hormone group compared with the placebo

group (Barnabei *et al.*, 2005). All types of bleeding were reduced after 1 year.

Endometrial hyperplasia

Endometrial hyperplasia may be simple, complex or atypical. The true incidence among women not taking hormones is unknown because women who do not bleed are unlikely to come under surveillance. The annualized incidence rates in the placebo groups of three trials were 0.56, 0.85 and 0 (PEPI Trial Writing Group, 1996; Speroff *et al.*, 1996; Pickar *et al.*, 2001). In the large WHI-EP study, 453 women in the placebo group agreed to have routine endometrial biopsy procedures. Of 368 who did have one or more biopsies during 5.6 years, 6 had endometrial hyperplasia (0.29% per annum; 95% CI 0.0, 1.5). In the remaining 7649 women in the placebo group during 5.6 years, 439 had an endometrial biopsy when indicated for bleeding, of whom 21 had endometrial hyperplasia (4.8% per annum; 95% CI 3.0, 7.3) (Anderson *et al.*, 2003). Thus, in women not taking hormones and not bleeding, endometrial hyperplasia rates are <1% per year; if there is bleeding, however, the rate is closer to 5% per year.

Unopposed estrogen use increases the risk of endometrial hyperplasia, and the addition of progestogen nullifies the increased risk (Lethaby *et al.*, 2004). The endometrial hyperplasia rate was >25-fold (95% CI 8, 76) in the CEE group of the PEPI trial ($P < 0.001$) compared with the placebo group (PEPI Trial Writing Group, 1996). Endometrial hyperplasia rates may be dose related: 0.4%, 3% and 8% with CEE dosages 0.3, 0.45 and 0.625 mg, respectively, within 12 months (Pickar *et al.*, 2001). With the use of estrogen–progestogen in the WHI-EP trial, endometrial hyperplasia rates were similar to the rates in the placebo group.

Endometrial cancer

The population rate of invasive endometrial cancer among women aged 50–69 is between 50 and 100 cases per 100 000 per year in most western countries and about a third of that figure in southern and eastern Asia, including Japan, and in most of Africa (Anderson *et al.*, 2003; Parkin *et al.*, 2005). Average risk among the 8102 placebo patients in the WHI-EP trial was slightly lower (31 cases in 5.6 years or 68 cases per 100 000 per year) (Anderson *et al.*, 2003). With the use of unopposed estrogen, endometrial cancer incidence is increased by 2.3-fold (95% CI 2.1, 2.5), although mortality is not significantly increased (Grady *et al.*, 1995). The use of estrogen and progestogen in the WHI-EP trial lowered the average risk but not significantly (27 cases in 5.6 years or 57 cases per 100 000 per year compared with 68 cases per 100 000 per year in the placebo group) (Table 6) (Anderson *et al.*, 2003).

Table VI. Hormone use and endometrial cancer (Million Women Study Collaborators, 2005)

Last exposure	Users	RR	95% CI
E only	14 204	1.45	1.02, 2.06
E + Cont P	69 577	0.71	0.56, 0.90
E + Cycl P	145 486	1.05	0.91, 1.22
Tibolone	28 028	1.79	1.43, 2.25

E, estrogen; Cont P, continuous progestogen; Cycl P, cyclic progestogen.

This is consistent with the information from a large observational study (Million Women Study Collaborators, 2005).

In summary, <5% of post-menopausal women experience vaginal bleeding. Estrogen and estrogen–progestogen increase the likelihood of bleeding. Unopposed estrogen use increases the risk of endometrial hyperplasia and endometrial cancer, but estrogen–progestogen does not increase either risk. The addition of progestogen to estrogen treatment to reduce endometrial cancer risk causes more breast cancers than the number of endometrial cancers it reduces (Millions Women Study Collaborators, 2005). Safer means are needed for the administration of unopposed estrogen in women who have a uterus.

Conclusions

Women today spend most of their reproductive life having repeated sterile cycles and menstruation. Associated with this, increase in menses has been an epidemic of menstrual complaints such as heavy menstrual bleeding and dysmenorrhea. The ability to manipulate the menstrual cycle by pharmacological means should allow women to choose when and if to menstruate. More research is needed on the acceptability of amenorrhea or long-interval cycles among contraceptive women.

Menstruation involves specialized mechanisms of tissue shedding, bleeding and hemostasis, corresponding in many ways to the inflammatory response. Increased knowledge of these processes would enable the development of specific treatments for endometrial bleeding.

Anovulatory bleeding is common in adolescence and may be more complicated in the presence of familial bleeding disorders. There is a need for studies of interventions to stop acute bleeding and treatments to control ongoing irregular bleeding.

Better knowledge of the mechanisms of heavy menstrual bleeding could lead to better medical treatment and reduce the reliance on surgery as a final resort for many women. Better diagnostic studies would help to determine whether fibroids and adenomyosis are causal factors or simply coincidental findings in women with bleeding.

Breakthrough bleeding on oral contraception may reflect the type of pill, the dose of hormone and the presence of follicles, or simply and commonly, missed pills. Breakthrough bleeding is unlikely to be due to sinister pathology in young women, where the management involves changing the pill formulation or the route of administration. There is a need for studies to determine which of these is the most effective.

Further research is needed on the treatment of BTB during the use of progestogen-only contraception, the mechanisms of progestogen-induced BTB, women's perceptions of bleeding and whether treatments for BTB can reduce discontinuation rates.

Estrogen and estrogen–progestogen increase the likelihood of bleeding in post-menopausal women. Studies are needed to find safe means to avoid the use of systemic progestogen during the administration of unopposed estrogen in women who have a uterus.

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