

1 Introduction

Menstrual problems are among the most common causes for GP and specialist referral, frequently accounting for one-third of gynaecological outpatient workload. The importance of menstrual disorder was acknowledged when the National Institute for Health and Care Excellence (NICE) commissioned a guideline on heavy menstrual bleeding (HMB), which was published in 2007.¹ Problems with menstruation are important since women today experience many more menstrual cycles during their reproductive life than they would have done 50 years ago. This is attributable to the fact that they have fewer pregnancies and also spend less time lactating. The average woman these days may expect 400 menstrual cycles in contrast to 40 in Victorian times.²

Women's lifestyles have also altered and it is not acceptable to suggest that menstrual problems are purely the woman's lot in life. Heavy periods can cause considerable inconvenience and are quite incompatible with the busy lifestyles of many women, who now expect swift and effective treatment for their problems.

It is of interest that the most common treatments vary from one country to another; in Sweden, for example, a woman's lifetime risk of having a hysterectomy performed is 12% whereas in parts of the USA it may be as high as 50%. Swedish women visit a gynaecologist with the expectation of receiving medical treatment; in many other parts of the western world they would expect a hysterectomy. This has considerable economic implications as well as suggesting that health education differs considerably around the world.

It is important that all gynaecologists have a basic understanding of menstrual reproductive physiology. This enables them to counsel women accurately and safely. Reassurance that there is no sinister pathology causing the problem is often all that is required, but such advice can only be given after appropriate investigation. Gynaecologists must also be in a position to offer up-to-date and appropriate treatment, which requires a thorough knowledge of the full range

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of options available. Some obtain information from guidelines either produced locally or nationally (for example, *Heavy Menstrual Bleeding* published by NICE).¹

This book discusses the aetiology of menstrual problems, their presentation and investigation as well as medical and surgical management. Specific problems such as fibroid-associated bleeding, adolescent and perimenopausal bleeding and breakthrough bleeding are covered, as are other critically important problems such as premenstrual disorders, pelvic pain and dysmenorrhoea. The individual chapters have been produced by those with a particular interest in the area who are also practising clinicians and thus have first-hand experience.

Terminology

Research into menstrual disorders has been complicated by geographical variation in the definition of commonly used terms that mean one thing in the USA and another in the UK, the term menorrhagia being a good example. This means that 'heavy menstrual bleeding' should be used instead of 'menorrhagia' as it describes the symptom and everyone knows what is meant, making it easier to compare studies. This topic was the subject of a recent workshop and is discussed at greater length in Chapter 2.³ The new terminology is becoming more accepted although inevitably it will take time.

Presentation

HEAVY MENSTRUAL BLEEDING (HMB)

The most common presenting menstrual problem is HMB. This complaint often follows a change in the woman's menstrual loss with an increase in flow which may have occurred relatively rapidly, or may have taken place over a number of years. It is difficult to assess the heaviness of flow clinically. It is well known that there is no correlation between the number of towels and tampons used and menstrual blood loss assessed objectively.⁴ It may be more appropriate to ascertain the degree of incapacity experienced, in that some women are unable to leave the house for 1 or 2 days each month because of the heaviness of menstrual flow, whereas others are less inconvenienced.⁵

HMB is defined in the NICE Guideline as follows: **'Bleeding that interferes with a woman's physical, social, emotional and/or material quality of life.'**¹

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‘Flooding’ may lead to significant problems particularly if it is sudden and unexpected; thus, some women who actually have a blood loss within the normal range and are not compromised from a health point of view are seriously inconvenienced. Passage of clots causes concern for many women as this is perceived as abnormal. A pictorial assessment chart has been developed for the assessment of menstrual loss, although it has not achieved widespread acceptability.⁶ However, it is very useful where objective evaluation is required.

MEASUREMENT OF MENSTRUAL BLOOD LOSS⁸

Investigations may be minimal in young women and hysterectomy must be virtually the only major operation carried out with no objective assessment of the problem. Blood loss can be measured easily but this is rarely done outside research projects, as collecting sanitary protection is not acceptable for many women. When blood loss is measured it yields fascinating information as it highlights those women whose problem is unlikely to have a physical basis, i.e. those complaining of HMB who have a menstrual blood loss of just a few millilitres. These women obviously have a problem but surgery may not be the most appropriate treatment for them. Measurement of haemoglobin is essential although menstrual problems can exist in the absence of anaemia. An assay of serum ferritin may be helpful.

A woman’s approach to her periods will vary through her reproductive life. After childbearing is completed, the view of the menses will alter dramatically. ‘Menstrual intolerance’ is a phrase that has been coined to describe those who simply want an end to their periods. This may be said in a rather derogatory fashion, but for the reasons described in the first paragraph it is probably quite understandable.

INTERMENSTRUAL INTERVAL (CYCLE LENGTH)

Women perceive a decrease in inter-menstrual interval as abnormal, although this is not the case (Figure 1.1). The longest intermenstrual interval occurs at the menarche; regular periods then tend to be established until a woman reaches her 30s, when the intermenstrual interval is likely to shorten.⁷ This is quite natural and the woman should be assured that there is nothing wrong with this (see Chapter 2 for a discussion of polymenorrhoea).

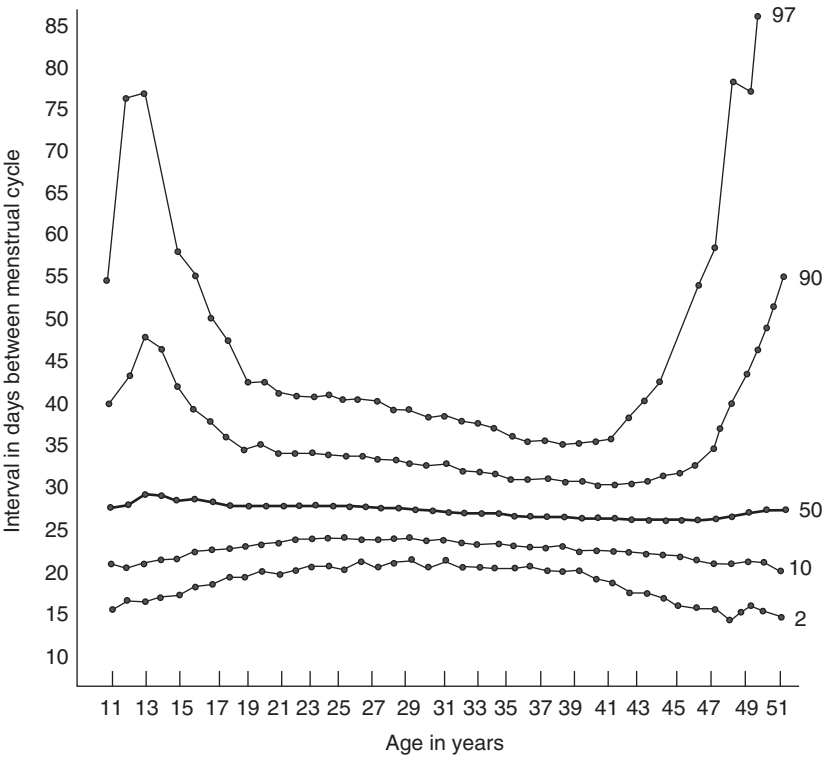


Figure 1.1 Menstrual cycles throughout the reproductive years; data from Treolar et al., 1967⁷

MENSTRUAL IRREGULARITY

Menstrual irregularity is a considerable nuisance for women because it leads to an unpredictable menstrual flow. It is most likely to occur at the extremes of reproductive life, the incidence of anovulation increasing as the menopause approaches. At the menopause unopposed estrogen production leads to persistent proliferative endometrium and occasionally hyperplastic change. This may be associated with extremely heavy bleeding at irregular intervals. Recently the menstrual cycle length has been used to predict the time and stage of the menopause.⁹

DYSMENORRHOEA

Dysmenorrhoea, or painful periods, may occur alone as the sole symptom in young, nulliparous women, or it may occur in conjunction with

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other menstrual problems, particularly in the older woman. Menstrual pain can be extremely debilitating, although overall the success rate for treatment is high. Division of dysmenorrhoea into primary and secondary is useful for the purposes of discussion although it can often be difficult to distinguish the two types on symptoms alone. Classical primary spasmodic dysmenorrhoea occurs at the onset of the menses and gets better after 1 or 2 days, whereas secondary dysmenorrhoea tends to start prior to the menses and worsens as it proceeds. However, there is considerable overlap between these two groups.

Any menstrual problem may be associated with premenstrual syndrome, although this is not discussed at length in this book. Premenstrual syndrome can often be successfully treated by therapies inducing anovulation. Many symptoms can be clustered premenstrually, including irritability, loss of concentration and emotional lability, as well as premenstrual headache, migraine and even epileptic fits. The treatment for these problems is particularly problematical, with no one specific treatment being successful.

ABNORMAL MENSTRUATION

The defects considered here are HMB and other menstrual abnormalities not particularly associated with infertility as the principal complaint, although endometriosis, fibroids and polycystic ovarian syndrome may be exceptions.

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2 Excessive menstrual bleeding

Excessive menstrual bleeding describes the clinical problems of heavy menstrual blood loss together with frequent or irregular menstruation. It is important that all gynaecologists have a basic understanding of menstrual reproductive physiology. This enables them to counsel patients accurately and safely. Reassurance that there is no sinister pathology causing the problem is often all that is required, but such advice can only be given after appropriate investigation. Gynaecologists must also be in a position to offer up-to-date and appropriate treatment, requiring a thorough knowledge of the full range of options available. This chapter addresses endometrial morphology, the mechanism of menstruation and the aetiology and management of menstrual problems.

Endometrial morphology

The human endometrium is a dynamic tissue that, in response to the prevailing steroid environment of sequential ovarian estrogen and progesterone exposure, undergoes well-characterized cycles of proliferation, differentiation and tissue breakdown on a monthly basis. If pregnancy fails to be established then the upper two-thirds of the endometrium (functional layer) is shed via menstruation. Endometrial regeneration then occurs from the basal layer.

There are three well-characterized phases of endometrial development: a preovulatory **proliferative** phase; a postovulatory **secretory** phase; and a **menstrual** phase involving tissue breakdown.

Endometrial dating has historically been related to the timing of ovulation. The series of classical morphological changes that occur in response to cyclical ovarian activity have been well detailed.¹ However, much controversy surrounds endometrial dating and some arguments suggest that histological dating, according to traditional histological methods, lacks both the accuracy and precision to provide a guide for clinical management. More robust methods for endometrial dating are likely to involve combining histological dating with reporting of last menstrual period and quantification of circulating estrogen and

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progesterone levels. Detailed gene microarray studies support this method for characterizing endometrial samples with consistency across these three parameters.²

It is also notable that exogenous administration of steroids produces a deviation from the classical histological features of glandular structure, mitotic status of glandular cells and secretions in the lumen of the glands³ when compared with accurately dated endometrium collected during a physiological cycle.

Mechanism of menstruation

The menstrual cycle is clinically described according to its regularity and duration of bleeding. The average length between menses is between 21 and 35 days with the duration of bleeding lasting 4–5 days.

During the luteal (secretory) stage of the menstrual cycle, in the absence of fertilization, there is regression of the corpus luteum, leading to a decline of the steroid hormone, progesterone. During the secretory phase, prior to this decline in circulating hormone levels, there is already a decline of endometrial sex steroid receptor expression in the superficial layer of the endometrium. The epithelial glands within the superficial layer of the endometrium are negative in their immunostaining for progesterone and estrogen receptors. It is therefore hypothesized that the declining levels of steroids can only be directly detected in the stromal cells of the superficial layer, which persistently stain for progesterone receptors.⁴ Additional evidence has demonstrated that menstruation can be blocked by progesterone add-back up to 36 hours after steroid decline.⁵ It would therefore appear that menstruation specifically occurs in response to the decline of progesterone levels.

In 1940, Markee⁶ was able to perform classical studies into the mechanism of menstruation. By transplanting explants of human endometrial tissue into the anterior chamber of a Rhesus monkey's eye, they were able to visualize direct events that occurred in response to progesterone withdrawal. In response to steroid decline, they observed stromal shrinkage, increased coiling of spiral arterioles and vascular stasis. These changes were followed by a period of vasodilation and perivascular bleeding and 24 hours later, a subsequent intense vasoconstriction and tissue necrosis prior to menstruation itself.

The molecular mechanism of menstruation in response to progesterone withdrawal is a complex cascade of events that have yet to be fully elucidated. It in part involves the production of prostaglandins that are able to induce vasoconstriction leading to a reduced blood flow to the endometrium. Subsequently there is increased expression of a range of locally acting mediators including cytokines, angiogenic

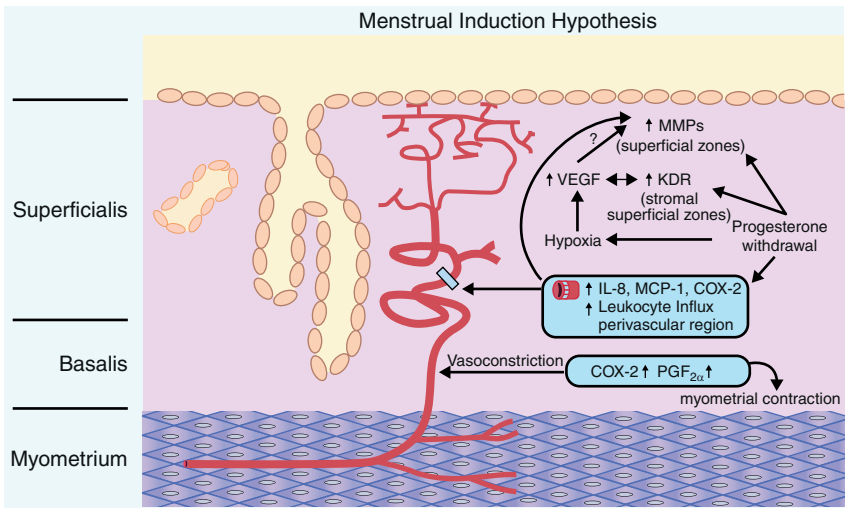


Figure 2.1 Hypothetical mechanism of menstruation. Adapted from Critchley, Kelly, Brenner, Baird. 2001 *Clin. Endocrinol.* 55: 701–10⁷

factors, protease enzymes and further prostaglandins. The cumulative endpoint of these changes in local mediators, together with an influx of migratory leukocytes is the process of menstruation. Figure 2.1 illustrates the hypothetical mechanism of menstruation.⁷

Coincident events of progesterone withdrawal and hypoxia Progesterone withdrawal results in an up-regulation of inflammatory mediators, production of matrix metalloproteinases and a leukocyte influx in the upper endometrial zones. There is coincident hypoxia and an up-regulation of matrix metalloproteinase production in the same endometrial upper zone stromal cells. Menstrual sloughing takes place from the superficial regions of the endometrium.

Aetiology of excessive menstrual bleeding

HEAVY MENSTRUAL BLEEDING

Menorrhagia is a clinical definition describing heavy menstrual blood loss. Heavy menstrual bleeding (HMB) has been accepted internationally as a more accurate terminology for this condition.⁸ This term shall be used in preference to menorrhagia during the rest of this section. HMB is defined as excessive menstrual blood loss, which can interfere with a woman's physical, social, emotional and/or material quality of life.⁹

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Unacceptable heavy menstrual blood loss affects 10%–30% of women of reproductive age and up to 50% of perimenopausal women.¹⁰ In the United Kingdom, 5% of women will seek help for this symptom annually and the risk of surgery performed for menstrual disorders is around 20%. In 2002–3, over 13 000 surgical procedures (hysterectomy and endometrial ablation) were performed in England for complaints of heavy bleeding.¹¹

In research studies, the objective definition of HMB is often based on measurement of menstrual haemoglobin content. Scandinavian studies demonstrated that the mean menstrual blood loss was around 40 ml and that regular menstrual blood loss in excess of 63 ml was associated with iron deficiency anaemia.¹² The 90th centile for measured blood loss was 80 ml and this has traditionally been taken as the upper limit of normal. However, in the clinical setting only 40%–60% of women with perceived heavy menstrual blood loss have an objective measurement of greater than 80 ml.¹³ It is therefore more appropriate to ascertain the degree of incapacity experienced, in that some women are unable to leave the house for 1 or 2 days each month because of the heaviness of menstrual flow, whereas others are less inconvenienced. ‘Flooding’ may lead to significant problems, particularly if it is sudden and unexpected; thus some women who actually have a blood loss within the normal range and are not compromised from a health point of view are seriously inconvenienced. Passage of clots cause concern to many women, as this is perceived as abnormal. A pictorial chart has been developed for the assessment of menstrual loss, although it has not achieved widespread acceptability.¹⁴ It is, however, used in many clinical trials either in its original or modified form.

The classification of abnormal uterine bleeding

A new classification system for causes of abnormal uterine bleeding (AUB) in the reproductive years was developed by the International Federation of Gynaecology and Obstetrics in November 2010. The system is based on the acronym PALM-COEIN¹⁵ that covers the causes of abnormal menstrual bleeding polyps, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory disorders, endometrial causes, iatrogenic. This novel classification was developed in response to concerns about the design and interpretation of basic science and clinical investigation that relates to the problem of abnormal uterine bleeding. This has led to much confusion when considering the results of clinical trials and also, methods of treating a particular problem, e.g. ‘menorrhagia’ meant different things on the two sides of the Atlantic and has now been replaced with Heavy Menstrual Bleeding.