Menorrhagia and its management

Over-the-counter tranexamic acid is likely to become available from some pharmacies in the next month, so pharmacists are more likely to be asked about heavy menstrual bleeding. Sally Haynes gives an overview of menorrhagia.

The absence of pregnancy during a menstrual cycle and the associated changes in hormonal activity result in menstruation, the sloughing off of the lining of blood and tissue (endometrium) that has built up in the uterus in preparation for an embryo to implant. A typical menstrual cycle will last between 21 and 35 days with menstruation lasting between three and eight days. Epidemiological studies show that, up until perimenopause, cycle length and duration of menstruation tend to decrease with age, and cycle regularity tends to improve. Other factors that can affect the menstrual cycle include rapid weight change, emotional stress and illness.

Menorrhagia and what is “normal”
Women cope with menstruation in different ways. Some, for example, may view period pains (dysmenorrhoea) as part and parcel of their monthly cycle. However, menorrhagia (excessive and prolonged uterine bleeding occurring at the regular intervals of menstruation) is one of the most common complaints affecting women of childbearing age.

Thirty per cent of women complain about heavy menstrual bleeding and 5 per cent of women aged from 29 to 44 years will consult their GP about heavy periods. Studies indicate that bleeding increases with age. Menorrhagia can also be a problem for peri-menopausal women.

Generally, total menstrual blood loss is between 35ml and 80ml. Losses over 80ml have been defined as heavy but in extreme cases, blood loss can be up to 500ml. However, it should be noted that heavy loss is subjective and, in practice, it should be defined by the woman’s assessment, as has been recommended by the National Institute for Health and Clinical Excellence 2007 clinical guideline on heavy menstrual bleeding.1

Some women might describe having to use tampons with sanitary towels, or having to change sanitary towels at least every two hours. They might complain of having large clots of menstrual blood or of prevention of normal daily activities, such as sport or going out, and they might also talk about feeling tired or appearing pale. Menorrhagia can also adversely affect sex life and lead to depression.

Mechanisms, causes and risk factors
The normal control of the endometrium, and thus the volume of menstrual loss, is complex. The endometrium undergoes a process of vascular and glandular proliferation, differentiation and regeneration with each menstrual cycle. Clearly, anything that increases the thickening of the endometrium, vascularisation or blood flow can potentially cause menorrhagia.

The thickness of the endometrium is controlled by oestrogen, which is released during the first half of the menstrual cycle. Vascular endothelial growth factor (VEGF), an endothelial cell-specific protein, is an oestrogen-responsive factor for angiogenesis that is also involved.

The endometrium produces and responds to prostaglandins. (The first prostaglandin identified was found in menstrual flow by an enthusiastic researcher who kept his daughter’s sanitary towels for research.) The fundamental actions of these prostaglandins are to inhibit or stimulate smooth muscle contraction, and to inhibit the release of noradrenaline. They affect both uterine and...
vascular smooth muscle and the net effect can be either an increase or decrease in blood loss, depending on the muscles affected. (Menorrhagia that is linked to prostaglandins is likely to be accompanied by period pains because of effects on muscle.) Inhibition of noradrenaline release will cause an increase in blood loss.

Increased menstrual loss can be a symptom of disease, but often there is no known cause. The presumption then is that the problem lies in chemical or hormonal control of the menstrual cycle.

In the absence of any underlying disease, heavy menstrual bleeding is called “dysfunctional uterine bleeding” (DUB) and, as Panel 1 shows, most women with menorrhagia fall into this category. A pathological cause (eg, a uterine tumour) requires treatment outside the scope of this article and Panel 2 lists symptoms suggestive of underlying disease that may require urgent referral.

Fibroids are benign tumours of the uterus associated with menorrhagia and are often treated by hysterectomy. Incidence increases with age (until menopause) and they are more common in black women than white women. Age and race are also related to risk of menorrhagia.

Drug treatment
Drug treatment should be the first-line option for women with menorrhagia and no symptoms suggestive of underlying disease. In general, a drug treatment should be given a three-month trial before changing to another or looking at non-pharmaceutical options.

In some cases, multiple treatments may be required since, as well as trying to find a long-term solution, it may be necessary to deal first with heavy bleeding that cannot be contained by normal sanitary protection (“flooding”).

The figure above gives an overview of a care pathway for a woman presenting with heavy periods, as described by NICE.

Haemostatic agents
The antifibrinolytic tranexamic acid has been shown to reduce menstrual blood loss by up to 58 per cent. It works by inhibiting plasminogen activators in the endometrium — levels of these enzymes, which change plasminogen to plasmin, are raised in menorrhagia. Plasmin dissolves fibrin clots. It is thought that the dissolution of clots adds to menstrual flow so tranexamic acid reduces menstrual blood loss.3,4

The normal dose is 1g three times a day for up to four days during menstruation. The maximum daily dose is 4g.

The main adverse effects of tranexamic acid are nausea, vomiting and diarrhoea. Thromboembolic events are rarely reported (but see below). More rarely, patients may report disturbances in colour vision and this is an indication to discontinue treatment.

The Medicines and Healthcare Products Regulatory Agency permitted reclassification of tranexamic acid as a pharmacy-only medicine in March 2010 and in the next few weeks Cyclo-F (500mg tranexamic acid tablets) will become available to the public. Points to note from this product’s summary of product characteristics are listed in Panel 3. Tranexamic acid has been available over the counter in Sweden since 1997. According to the MHRA reclassification assessment,4 the drug is not thrombogenic and does not induce a general prothrombotic state. (Swedish studies indicate that incidence of thrombosis is comparable to frequency of spontaneous thrombosis in the general population.) It points out that a Royal College of Obstetricians and Gynaecologists guideline recommends that before treatment a history of heavy clinical menstrual blood loss should be obtained, an abdominal and pelvic examination should be performed, and a full blood count should be obtained but recognises the argument that most GPs do not carry out a pelvic examination or full blood count in patients presenting with menorrhagia. “In addition, it is sub-mucous fibroids that are assumed to cause menorrhagia; and these can only be detected by ultrasound scan and/or hysteroscopy; therefore the benefit of vaginal examination by GPs is said to be questionable,” it adds.

The haemostatic drug etamsylate (Dicyne) is also licensed for use in menorrhagia. It is thought to act by increasing capillary vascular wall resistance and platelet
NSAIDS Both prostaglandin E2 synthesis
and prostaglandin E2 binding sites are known to be increased in women who suffer from
menorrhagia. This makes NSAIDS a logical
treatment choice due to their inhibition of
cyclooxygenases that play an important part
in prostaglandin production. In addition, they
are useful when dysmenorrhoea co-exists.

NSAIDS have been shown to reduce blood
loss by 20–50 per cent but mefenamic acid is
the only one licensed for treating
menorrhagia. Mefenamic acid remains the
most effective choice because it has a dual
action, both reducing prostaglandin synthesis and inhibiting binding of prostaglandin E2 to
its receptor. The normal dose is 500mg three
times a day, starting on the first day of heavy
bleeding. Although its summary of product
characteristics states that it can impair female
fertility, this should not be an issue for short-
term use in menstruation.

Mefenamic acid can be combined with
tranexamic acid if menstrual bleeding and
dysmenorrhoea are problematic but the
combined dosage schedule may make this
option unacceptable to many women, especially with the need to time medication
with food.

Ibuprofen and naproxen are licensed for
use in dysmenorrhoea but not in menorrhagia.
However each has been shown to reduce
bleeding. There is also evidence for the
effectiveness of indometacin and flurbiprofen
in reducing blood loss. There is no evidence to
support the use of cyclo-oxygenase 2 inhibitors and none is licensed for this
indication.

The side effects of NSAIDS are well
known but in a predominantly young population and with intermittent use they
should not be a problem.

Hormonal treatment If the woman requires
contraception, hormonal treatments are an
option.

Intrauterine levonorgestrel The
levonorgestrel intrauterine system (LNG-
IUS) reduces blood loss by up to 95 per cent.
It also relieves dysmenorrhoea, and provides
reliable contraception. It is especially useful if
long-term contraception (anticipate at least 12
months) is required and the combined oral
contraceptive is contraindicated. It can be kept
in place for five years. The LNG-IUS has
been shown to be superior to other drugs in
randomised controlled trials.

The LNG-IUS is generally well tolerated
but significant side effects can develop,
including oedema, weight gain, headache,
depressive mood, abdominal and pelvic pain,
acne, dysmenorrhoea and vaginal discharge.
In addition, any intrauterine device can cause
an increase in menstrual loss and spotting.

Insertion of the device can cause pain,
which normally responds to NSAIDS. Uterine
perforation is also a risk during insertion.

Once in situ there is a risk of infection of
between 1:100 and 1:1,000.

Combined oral contraceptive The
combined oral contraceptive pill is accepted as the first-line treatment when relatively short-
term contraception is required (see later). This
is thought to work by inducing regular
shedding of a thinner endometrium. It will
also reduce associated dysmenorrhoea and
regulate menstrual cycles. However there is
little trial data to support use for its
menorrhagia — a Cochrane review was unable to achieve its object because of the
paucity of data. Also the data that do exist
involve higher dose preparations containing
50g ethinylestradiol. A small study found no
significant difference between groups treated
with a combined oral contraceptive, mefenamic acid, low dose danazol or
naproxen but, overall, the evidence from this
one study is not sufficient to assess efficacy.

In terms of combined treatments, an
NSAID may be used with a combined oral
contraceptive where dysmenorrhoea is
problematic but Clinical Knowledge
Summaries advises against the prescribing of
tranexamic acid with a combined oral
contraceptive or the LNG-IUS.

Progestogen-only treatment Norethisterone is recommended for 21 days
each cycle, starting from day 5, to cover the
follicular and luteal phases. The dose
(licensed) is relatively high, at 5mg tds.
According to CKS and NICE, the licensed
regimen of oral norethisterone for DUB, 5mg
two to three times a day used only during the
luteal phase (ie, from day 19 to day 26 of the
cycle) is no longer recommended because it is
ineffective. (The British National Formulary
includes a licensed dose of norethisterone for
menorrhagia, 5mg twice daily from day 19 to
day 26 of the menstrual cycle, but
acknowledges the relative ineffectiveness of
this regimen compared with other treatments
(BNF 60, section 6.4.1.2, Progestogens].)

High dose norethisterone (eg, 30mg a day
[unlicensed] until bleeding stops, then reduce
the dose by 5mg a day) has been used to stop

PANEL 1: CAUSES AND
OCCURRENCE
• No known cause (eg, dysfunctional uterine
bleeding) >60 per cent of cases
• Gynaecological (eg, endometrial cancer,
ovidian tumours, endometriosis, fibroids or
polyps, chronic pelvic inflammatory disease)
>30 per cent of cases
• Endocrine and haematological (eg, thyroid
disorders, clotting abnormalities, platelet
disorders) <5 per cent of cases

PANEL 2: SYMPTOMS THAT
NEED TO BE REFERRED
• Irregular bleeding
• An increase in blood loss that is different
from what is normal for the woman (unless
due to an intrauterine contraceptive device)
• Intermenstrual bleeding
• Postcoital bleeding
• Pain during intercourse (dyspareunia)
• Pelvic pain
• Premenstrual pain (eg, headache, backache,
joint and muscle pain)

PANEL 3: POINTS TO CONSIDER IF SUPPLYING CYCLO-F OTC
• The woman must have regular (no more than three days variation
in cycle duration) 21 to 35 days cycles and be 18 years or over.
• Use can continue as long as periods remain heavy and regular
but women who do not experience reduced bleeding within three
menstrual cycles should consult their GP.
• Contraindications include irregular menstrual bleeding, kidney
problems (higher risk of blood clots), thromboembolic disease
(including family history), use of anticoagulants, anaemia, use
of oral contraceptives, pregnancy and breastfeeding (tranexamic
acid crosses the placenta and is present in breastmilk).
• Cautions include women over 45 years, those who are obese and
diabetic (they may be at greater risk of endometrial cancer and
thromboembolic disease), those who have polycystic ovary
syndrome or history of endometrial cancer (in a first degree relative) and those taking tamoxifen
(increased risk of endometrial cancer) or unopposed oestrogen therapy (these women should not
be having periods). These women should consult their GP before starting treatment.

* Adapted from CymoF Summary of product characteristics
A large number of websites offer information on complementary and alternative remedies for menorrhagia. A lot of the advice seems to be aimed at women experiencing problems around the menopause when acute menorrhagia can become a problem and there is no clear evidence for the efficacy of any of the recommended products. For example, black cohosh has been used for menorrhagia and is known to be safe but there is no good evidence for its efficacy. Phyllanthus has also been used.

Complementary therapies

Conclusion

Practice points

Reading is only one way to undertake CPD and the regulator will expect to see various approaches in a pharmacist’s CPD portfolio.

1 When women purchase over-the-counter treatments for period pain, ask about any symptoms of menorrhagia.

2 Ask about symptoms of anaemia when supplying treatments for menorrhagia.

3 Make sure your staff are aware of the availability of OTC tranexamic acid.

Consider making this activity one of your nine CPD entries this year.

References


2 Willacy H. Menorrhagia. Available at www.patient.co.uk (accessed on 13 January 2011).

3 Meda Pharmaceuticals. Cyclo-F patient information leaflet.


7 Rees M (2004) personal communication

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