

Modern management of menorrhagia

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Abstract

Menorrhagia, defined clinically as menstrual blood loss in excess of 80 ml per cycle, is a common gynaecological complaint that presents both to primary and secondary care. The aim of this review of the literature is to discuss current opinion in the investigation and management of menorrhagia. As menorrhagia is a subjective condition that is difficult and impractical to assess objectively, this review incorporates patient-centred outcomes such as patient satisfaction and continuation with treatment together with more traditional outcomes such as percentage reduction in menstrual loss. As there are many treatment options available, with no one option being superior in all respects, patient choice and treatment preferences should be taken into account when deciding upon management.

Key message points

- Menorrhagia is the commonest gynaecological problem presenting to both primary and secondary care.
- There are many effective treatments available for menorrhagia.
- Women should be assisted to make informed decisions about management, by discussing the risks and benefits of each treatment.

Introduction

Menorrhagia, defined as excessive menstrual blood loss (MBL) in excess of 80 ml per period,¹ has an enormous impact on women's lives and is a common reason why women consult both general practitioners (GPs) and gynaecologists.² Over 5% of women aged 30–49 years consult their GP each year with this complaint and 12% of all referrals to gynaecology outpatient departments are to investigate and treat menorrhagia.^{3,4}

Every year over 800 000 prescriptions are written for this condition in England and Wales, and more than 90 000 hysterectomies and endometrial ablations are performed, of which two-thirds are undertaken in women presenting with menorrhagia.¹ Even though the great majority of women referred to gynaecologists with this condition have no underlying pathology or abnormality, many women are prepared to subject themselves to potent medical or surgical intervention.⁵

The aim of this review of the literature is to discuss current opinion in the investigation and management of menorrhagia. This review is concerned with the management of heavy menstrual bleeding for which no underlying cause has been identified (more than 50% of cases); the management of underlying causes, such as pelvic pathology, endocrine disorders or clotting disorders, are beyond the scope of this review.

Methods

Electronic databases, MEDLINE, EMBASE and The Cochrane Library were searched, using search terms

including menorrhagia, treatment and related terms. Amongst the many articles retrieved were five Cochrane Reviews, and one very recent review by Oehler and Rees; the bibliographies of these articles were also used. These articles form the base upon which this review is written.^{6–11}

This review considers briefly the investigation and diagnosis of menorrhagia followed by a review of current treatment. Treatment can be broadly divided into medical and surgical treatments, which are both discussed.

Menorrhagia is defined clinically as MBL in excess of 80 ml per cycle, and guidelines for treatment are based on this definition. This definition was taken from Scandinavian population studies of MBL.¹² However, it is widely accepted that as well as it being impractical to measure MBL outside of research studies, there is no correlation between women's subjective assessment of their blood loss as heavy, and their actual blood loss, which is often less than 80 ml.^{13,14}

Although management guidelines recently produced have acknowledged this discrepancy by discussing the importance of patient perception and patient quality of life, the treatment emphasis is still aimed at reducing blood loss.^{1,15} Much of the research looking at the efficacy of treatments for menorrhagia has therefore focused on reduction of MBL as an outcome. Much less work has been done including patient-centred outcomes which, in this highly subjective condition, might be considered equally important.^{16,17} In this review, patient-centred outcomes such as patient satisfaction and continuation with treatment have been incorporated, and are represented in Table 1. This table aims to answer patient questions such as 'Does it work and will I experience any side effects?' rather than simply percentage reduction in MBL.

Diagnosis and investigation of menorrhagia

Menstrual history

As menstrual loss is self-reported and subjective, and routine objective measurements are impractical, a detailed menstrual history is vital to the diagnosis of menorrhagia. Specifically the patient should describe a history of heavy MBL over several consecutive cycles, without any intermenstrual or postcoital bleeding.¹⁵ Symptoms suggestive of other pathology or risk factors for endometrial cancer should be sought (see Box 1), and if present will require different management and possibly referral to secondary care for further investigation.

Box 1: Risk factors for endometrial cancer

- Tamoxifen
- Unopposed oestrogen treatments
- Polycystic ovarian syndrome
- Obesity

Table 1 Effectiveness of menorrhagia treatments

Treatment	Symptoms improved ^a	Unwanted side effects ^a	Perioperative complications ^a	Further treatment ^a	Intermenstrual bleeding ^a	References
Watchful waiting	20.7 (20–21.4)	NA	NA	NA	NA	Edlund et al. (1995) ²⁵ , Grover et al. (1990) ²⁸
Non-hormonal drugs	72.5 (54–86)	16.7 (4–33)	NA	NA	NA	Bonnar and Sheppard (1996) ²⁴ , Edlund et al. (1995) ²⁵ , Grover et al. (1990) ²⁸ , Winkler (2003) ²⁷
Hormonal drugs	44 (44)	17	NA	NA	NA	Irvine et al. (1998) ³¹ , Iyer et al. (2002) ⁶
LNG-IUS (Mirena®)	79.7 (68–89)	59.7 (55–63)	NA	NA	22	Crosignani et al. (1997) ³³ , Hurskainen et al. (2001) ³⁵ , Lethaby et al. (2003) ¹⁰ , Stewart et al. (2001) ⁴⁹
Endometrial ablation	84 (80–87)	NA	13 (12–15)	29 (22–38)	NA	Aberdeen Group (1999) ⁴⁸ , Lethaby et al. (2002) ⁸ , O'Connor et al. (1997) ⁴¹ , Pinion et al. (1994) ⁴⁴
Abdominal hysterectomy	100	NA	33 (15–51.2)	NA	NA	Al-Kadri et al. (2002) ³⁷ , Benassi et al. (2002) ³⁸ , Carlson (1997) ³⁹ , Meltomaa (1999) ⁴⁰ , O'Connor et al. (1997) ⁴¹ , Ottosen et al. (2000) ⁴²
Vaginal hysterectomy	100	NA	26.7 (16.5–41.9)	NA	NA	Al-Kadri et al. (2002) ³⁷ , Benassi et al. (2002) ³⁸ , Carlson (1997) ³⁹ , Meltomaa (1999) ⁴⁰ , O'Connor et al. (1997) ⁴¹ , Ottosen et al. (2000) ⁴²

^aThe values given are the mean percentage with the range in parentheses. LNG-IUS, levonorgestrel-releasing intrauterine system; NA, not applicable.

Examination and preliminary investigations

An abdominal and pelvic examination is required to exclude uterine enlargement (of >10 weeks' gestation size), pelvic masses or tenderness, all of which may indicate other pathology. Cervical cytology may be included if not up to date, and a full blood count is recommended to determine the degree of anaemia. There is no need for other blood tests, such as thyroid function tests or an anticoagulation screen, unless these are indicated by the presence of other clinical symptoms.

If the results of examination and investigation are normal, and any iron-deficient anaemia treated, reassurance or 'watchful waiting' may be all that the woman requires. If the woman still finds her menstrual flow unacceptable, the Royal College of Obstetricians and Gynaecologists (RCOG) Guidelines suggest that medical management should be tried for at least 3 months prior to referral to secondary care.¹⁵

Further investigation

The first step in the investigation at secondary care should be a transvaginal ultrasound scan.^{11,18} This is a non-invasive, non-painful method for selecting those women in need of further diagnostic evaluation. It has a sensitivity of 80% and a specificity of 69% for detecting endometrial thickness, polyps and myomata.¹⁹ A meta-analysis of studies in menopausal women showed that endometrial thickness, as measured by ultrasound, has a sensitivity of over 96% for detecting endometrial cancer.²⁰ Although this sensitivity has not been demonstrated in premenopausal women, the RCOG Guideline Development Group suggests that transvaginal sonography should be used as a useful screening tool prior to more invasive procedures and conclude that an endometrial thickness of 10–12 mm represents a reasonable cut-off in premenopausal women.¹⁸

The next stage of investigation would be endometrial biopsy (with or without hysteroscopy) to exclude malignant or premalignant disease. All women who have any of the risk factors for endometrial cancer (see Box 1) should have endometrial sampling; also women in whom

medical treatment has been unsuccessful may be considered. A meta-analysis by Spencer et al. examining different methods of endometrial sampling did not uniformly support one method, however no method will sample the entire uterine cavity.²¹

The most common methods of endometrial sampling include dilatation and curettage (D&C), endometrial biopsy and hysteroscopy. The previous gold standard method of D&C has now been replaced by endometrial biopsy. Unlike D&C, endometrial biopsies do not require a general anaesthetic, and have fewer complications. The RCOG have suggested that there is no longer a place for traditional D&C either in the investigation or in the treatment of abnormal uterine bleeding.¹⁸ As the technical skills required for endometrial biopsy are similar to those required in inserting intrauterine contraceptive devices (IUDs), some authors have argued for their use in primary care.¹¹

However, whilst endometrial biopsy is the method of choice for diagnosing or excluding malignancy, it is still a blind procedure and as such unsuitable for detecting other possible causes of abnormal uterine bleeding such as endometrial polyps or submucosal myomas, and a combination of methods is required. The RCOG Guideline Development Group suggest that in those women referred to secondary care, transvaginal sonography is first performed. If this is normal, then an endometrial biopsy may be taken; if the sonography is abnormal, they suggest a biopsy and direct visualisation using hysteroscopy.

Medical treatment

As was discussed above, some women may benefit simply from reassurance that their experiences are not abnormal, and a 'watchful waiting' approach may be an appropriate first step.²² If further treatment is warranted the Guidelines from the RCOG recommend that at least one non-surgical treatment should be tried, for a minimum of 3 months before referral for a gynaecological opinion.¹⁵

Medical treatment for menorrhagia can be divided broadly into hormonal and non-hormonal treatments.

Non-hormonal treatments

Non-hormonal treatments of menorrhagia include non-steroidal anti-inflammatory drugs, reducers of capillary fragility and antifibrinolytics.

Non-steroidal anti-inflammatory drugs (NSAIDs). Numerous studies, including a recent Cochrane meta-analysis, have examined the efficacy of NSAIDs, and found no evidence that any one NSAID is superior to the others.⁹ Mefenamic acid has been the most extensively studied, on account of its property of inhibiting prostaglandin synthesis and binding to prostaglandin receptors, which are increased in women in menorrhagia, and therefore included in one of the many theories of causation.^{11,23} Trials looking at MBL have found reductions ranging from 22% to 46%.^{9,24}

Common side effects of NSAIDs are gastrointestinal symptoms, and the different NSAIDs have slightly different side effect profiles. Mefenamic acid is less likely to induce gastrointestinal side effects than naproxen, but all NSAIDs are contraindicated in women with peptic ulcer disease. Although dosage varies depending on the NSAID used (mefenamic acid 250–500 mg and naproxen two to four times/day, ibuprofen 200–400 mg three times/day) all are usually taken when menstruation commences and continued for 5 days, or until menstruation ceases, and have the additional benefit of alleviating menstrual pain.

Reducers of capillary fragility. Ethamsylate is a drug thought to act by reducing capillary fragility in the endometrium, however the evidence is conflicting and inferior to NSAIDs and tranexamic acid. Its use is not recommended in the UK.¹⁵

Antifibrinolytics. Women with heavy menstrual bleeding have also been found to have increased levels of the enzymes that cause fibrinolysis; antifibrinolytic drugs (of which tranexamic acid is the main example) have therefore been promoted for the treatment of menorrhagia.¹¹ Tranexamic acid has been found to reduce MBL by up to 50%.^{7,25} Studies comparing tranexamic acid to NSAIDs and ethamsylate found tranexamic acid to be superior in terms of MBL.^{7,24}

Side effects of tranexamic acid are similar to those of NSAIDs and again are dose-dependent. Fears regarding increased venous thromboembolism have been shown to be unfounded by long-term studies in Scandinavia, which concluded that the incidence of thrombosis in women treated with tranexamic acid is no different to that of the spontaneous incidence in the female population.²⁶ Tranexamic acid (1 g three times/day for 4 days) is also taken only during menstruation which, as well as aiding compliance, means that it is suitable for women who are trying to conceive.

Trials which included patient-centred outcomes, such as satisfaction with treatment or symptoms controlled, found a 'symptoms better' rate of between 54% and 86% (Table 1).^{24,25,27,28} Thus antifibrinolytic treatment should be considered as a first-line treatment for menorrhagia.

Hormonal treatments

Oral progestogens. Progestogens are commonly used in the treatment of menorrhagia, with different efficacies depending on the dose or the route of administration. Least successful is the use of low-dose cyclical oral progestogens (for 5–10 days). Trials comparing this regime with NSAIDs, tranexamic acid, danazol or progestogen IUDs have found it ineffective, and it is not recommended by the RCOG.^{10,15,29} Unfortunately GPs still commonly prescribe it.³⁰

Higher dose progesterone (5 mg norethisterone tds) prescribed from Day 5 to Day 25, can lead to a significant reduction in MBL,³¹ and very large doses (30 mg daily) can be used to stop torrential bleeding, usually within 24–48 hours from when the dose can be reduced. Common unwanted effects, which are dose dependent, include weight gain, breast tenderness and headaches.

Combined oral contraceptive pills (COCs). Clinical experience suggests that COCs can be used successfully in the treatment of menorrhagia. However a recent Cochrane systematic review found that no large, well-conducted, randomised controlled trials have taken place.⁶ The one small study that they did find showed a reduction in MBL of 43%.²⁹ Older women are disinclined to take COCs partly out of fear of thromboembolic events, but in women with no other risk factors (such as smoking or family history of thromboembolic events) age alone is not a contraindication. Also the regime is familiar to many women, and has the added benefit of contraception.

Androgens. Androgens such as danazol or gestrinone have been shown to reduce MBL by up to 80%,³² however their use is limited by androgenic side effects experienced by up to 75% of women taking them. These include weight gain, skin problems such as acne, and deepening of the voice and therefore preclude long-term therapy. They can be used in the short term for women awaiting surgery, and have been used as an endometrial-thinning agent prior to endometrial ablation.

Gonadotrophin-releasing hormone agonists (GnRH agonists). GnRH agonists administered continuously create a hypogonadotrophic state by down-regulation, which in turn leads to a hypo-oestrogenic state, frequently inducing amenorrhoea. However again treatment is limited by side effects. Side effects associated with a hypo-oestrogenic state include rapid bone demineralisation and menopausal symptoms such as vaginal dryness and hot flushes, which reduce quality of life. Again they have been used successfully as preoperative endometrial thinning agents, but side effects usually preclude their long-term use.

Intrauterine progestogen. This involves fitting an IUD that is impregnated with a progestogen. A commonly used device is the levonorgestrel intrauterine system (LNG-IUS) known as the Mirena[®]. Trials comparing the LNG-IUS to oral progestogens have found it to be superior, reducing MBL by up to 96%.^{10,31,33}

The LNG-IUS has also been compared in trials with surgical treatments such as transcervical resection of the endometrium (TCRE) and in women on the waiting list for hysterectomy.^{33,34} Compared to TCRE the mean reduction in MBL was less, but the patient-centred outcome of patient satisfaction was the same.³³ A significant proportion of women in the LNG-IUS group on the waiting list cancelled their hysterectomy (64%) compared to those in the medical treatment group (14%).³⁴

The main unwanted effect of the LNG-IUS is frequent and variable intermenstrual bleeding, particularly in the first 3 months of treatment. Prewarning of this side effect before fitting the IUS is essential. The LNG-IUS is also very effective, reversible contraception. Some authors consider the LNG-IUS to be a serious alternative to surgical management of menorrhagia, with the added benefits of being cheaper and preserving fertility.³⁵

Surgical treatment

Surgical treatment may be necessary where there is pelvic pathology as a cause of heavy menstrual bleeding, such as

polyps or endometriotic masses, but these procedures are not specifically covered in this review. Surgery is also indicated when medical treatment is not tolerated, ineffective or when it is the patient's choice. There are two main types of surgery used in the management of menorrhagia, namely hysterectomy and endometrial ablation.

Hysterectomy

Hysterectomy is the most common major operation carried out on women in the UK, with more than 90 000 operations performed in the UK every year, and at least 50% of these are for menorrhagia. Hysterectomy cures menorrhagia and results in generally high patient satisfaction,³⁶ however it is a major operation with associated morbidity and mortality, and high service costs.

Broadly speaking, hysterectomy can be performed either through the abdominal approach, entailing an abdominal incision, or vaginally, either with or without the use of a laparoscope. Complication rates for laparoscopic techniques are similar to complication rates found with the vaginal approach.

Abdominal hysterectomy is associated with a significant perioperative complication rate ranging from 15% to 52%, and vaginal hysterectomy has a slightly lower, but still significant, perioperative complication rate of 16.5% to 41.9%.^{37–42} There is also a small mortality rate associated with hysterectomy, which cannot be ignored in an elective procedure such as hysterectomy for menorrhagia. This ranges from 6 to 11 per 10 000 cases of hysterectomy for non-obstetric and non-malignant conditions.⁴³ In addition, there have been concerns regarding possible long-term sequelae such as sexual dysfunction, early ovarian failure and bowel adhesions, which have led to the investigation of numerous surgical alternatives to hysterectomy in recent years.¹¹

Endometrial ablation

The term endometrial ablation encompasses all surgery that selectively destroys the endometrium. There are many techniques for achieving this, the concept of which is to remove the endometrium up to and including the basal layer in order to induce amenorrhoea. The most common method of endometrial ablation is TCRE, excising the endometrial lining using a wire loop, roller-ball or a laser. The roller-ball technique is considered to be the gold standard by most experts in this field as this has a lower risk of uterine perforation.¹¹ The effects of TCRE are long term, so it is not a method that is suitable for women who have not yet completed their family. As it is still possible to conceive, alternative methods of contraception must be considered.

There is a 12–15% perioperative complication rate associated with TCRE and also, because of the regenerative nature of the endometrium, a significant proportion of women will need further treatment for menorrhagia within 4 years of the original TCRE.^{8,41,44} There is evidence that the use of GnRH agonists or danazol as short-term preoperative thinning agents improves the outcome of TCRE.⁴⁵

There have been many other less invasive techniques used for endometrial ablation in an effort to reduce the necessary skill required for hysteroscopic surgery such as those described above. These include thermal balloon therapy, hydrothermablation, radiofrequency electrosurgery, microwave endometrial ablation and others. The idea is the same, namely to destroy the endometrial lining and induce amenorrhoea, though the techniques differ. With the thermal balloon a balloon is inserted into the uterine cavity and filled with hot water. Some trials

have shown this to be as effective as standard TCRE techniques.⁴⁶ Hydrothermablation is free fluid instilled into the uterine cavity and heated to the appropriate temperature to ablate the endometrium. Radiofrequency electrosurgery uses alternating current, and microwave ablation is a further new technique using microwave energy.

Several randomised controlled trials have compared the outcomes of endometrial resection and ablation versus hysterectomy, and these have been summarised in a Cochrane review.⁸ Hysterectomy had a greater improvement in MBL, and better rates of patient satisfaction, but quality of life measures were not markedly different. Endometrial ablation has considerable short-term benefits compared to hysterectomy, such as shorter hospital stays, reduced postoperative complications and lower direct costs; however due to the relatively large proportion of women requiring further treatment after ablative procedures, the difference in costs narrows over time.

Conclusions

Menorrhagia is the commonest gynaecological problem presenting both to primary care professionals and in routine gynaecological outpatient departments. The management, once other pathology has been excluded, should aim to reduce menstrual flow, improve the quality of life and reduce the likelihood of iron deficiency anaemia. In order to achieve this there are a variety of options as outlined above.

In the management of menorrhagia in particular, the RCOG states that women's preferences should be taken into account in deciding upon treatment.¹⁵ The *Effective Health Care Bulletin* directed that, since no one option is superior in all respects, women should be assisted to make informed choices about their treatment.¹

It is important, therefore, that in counselling women regarding their management and treatment options for their menorrhagia, that the risks and benefits for each treatment are discussed, to allow women to be in a position to state their preferences.⁴⁷

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