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Benefits and Risks of Pharmacological Agents Used for the Treatment of Menorrhagia

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Abstract

Menorrhagia affects the lives of many women. The assessment of menstrual flow is highly subjective and gauging the severity of the condition by objective assessment of menstrual blood loss is impractical. In treating menorrhagia, the primary aim should be to improve quality of life. Women are willing to undergo quite invasive treatment in order to achieve this. Drug therapy is the initial treatment of choice and the only option for those who wish to preserve their reproductive function. Despite the availability of a number of drugs, there is a general lack of an evidence-based approach, marked variation in practice and continuing uncertainty regarding the most appropriate therapy. Adverse effects and problems with compliance also undermine the success of medical treatment. This article reviews the available literature to compare the efficacy and tolerability of different medical treatments for menorrhagia.

Tranexamic acid and mefenamic acid are among the most effective first-line drugs used to treat menorrhagia. Despite being used extensively in the past, oral luteal phase norethisterone is probably one of the least effective agents. Women requiring contraception have a choice of the combined oral contraceptive pill, levonorgestrel-releasing intrauterine system (LNG-IUS) or long-acting progestogens. Danazol, gestrinone and gonadotropin-releasing hormone analogues are all effective in terms of reducing menstrual blood loss but adverse effects and costs limit their long-term use. They have a role as second-line drugs for a short period of time in women awaiting surgery.

While current evidence suggests that the LNG-IUS is an effective treatment, further evaluation, including long-term follow up, is awaited. Meanwhile, the quest continues for the ideal form of medical treatment for menorrhagia – one that is effective, affordable and acceptable.

Menorrhagia, or excessive menstrual bleeding, prompts 1 in 20 women of reproductive age to seek medical advice each year in the UK.[1] It accounts for 60% of primary-care consultations for menstrual problems[2] and 12% of all gynaecology referrals.[3] It can disrupt day-to-day work and social commitments and has a major impact on quality of life.[4]

Defining menorrhagia is problematic, and it can be difficult to reconcile subjective and objective interpretations of severity of disease. Menorrhagia is defined as blood ≥80mL per menstrual cycle.[5,6] However, objective measurements of menstrual volume do not necessarily correspond to women's perceptions of the severity of bleeding. Many women who seek treatment lose less than the statutory 80mL per cycle.[5,7] In a national survey, 31% of women described their menstrual loss as heavy.[8] Thus despite a traditional emphasis on objective methods of evaluating menstrual loss, this is often impractical within the context of research studies, and a woman's subjective perception of her condition remains a crucial factor influencing her referral and subsequent treatment.

The commonest cause of menorrhagia is dysfunctional uterine bleeding,[9] although fibroids and adenomyosis are also frequently encountered. The effective treatment of menorrhagia should aim to relieve symptoms and improve quality of life while minimising adverse effects,[10] and while medical management remains the first-line of therapy, there continues to be some uncertainty about its effectiveness and acceptability. Approximately 60% of women with menorrhagia undergo hysterectomy within 5 years of referral to a gynaecologist.[11] Few choose to continue medical treatment,[11] despite the fact that 80% of them have no demonstrable pelvic pathology and over one-third of hysterectomies for heavy menstrual bleeding result in the removal of anatomically normal uteri.[12,13] In the last decade, endometrial ablation has provided a conservative surgical alternative to hysterectomy. Recent follow-up data from a trial of transcervical resection of the endometrium (TCRE) versus medical treatment revealed that only 10% of women who were allocated to medical treatment chose to continue with it after 5 years.[14] The decision to discontinue medical treatment may be due to genuine lack of effectiveness; alternatively, it could be related to inappropriate and non-evidence-based use of drugs.[15] Despite the availability of a variety of agents for heavy menstrual bleeding, there is marked variation in practice and ongoing debate about the most appropriate therapy.[16,17]

This article reviews the available literature to evaluate the efficacy and tolerability of different pharmacological agents used for the treatment of heavy menstrual bleeding. These agents included non-hormonal and hormonal treatments (table I). A literature search was performed in order to identify systematic reviews and primary randomised trials. Data from observational studies were obtained in areas where no randomised trials could be found. Databases searched included MEDLINE (1966 to July 2002), Embase (1980 to July 2002) and the Cochrane Library. Key words used were menorrhagia, uterine haemorrhage, dysfunctional uterine bleeding, menorrhagia/drug therapy, menorrhagia/

Table I. Pharmacological agents used for the treatment of menorrhagia

Non-hormonal
NSAIDs
Antifibrinolytics
Etamsylate
Hormonal
Progestogens
Cyclical progestogens (oral progestogens given in luteal phase or in 21 days of a 28-day cycle)
Progestogen-releasing intrauterine systems
Long-acting progestogens (injectable or implants)
Combined oral contraceptives
Danazol
Gestrinone
Gonadotrophin-releasing hormone analogues

Table II. Efficacy and tolerability of individual pharmacological treatments for the treatment of menorrhagia

Outcome	Reduction of menstrual blood loss	Adverse effects	Additional beneficial effects
Mefenamic acid	20–50%[20]	Gastric intolerance, nausea, vomiting bronchospasm	Use during menstruation. Improves dysmenorrhoea and menstrual migraine
Tranexamic acid	47–54%[25]	Nausea, vomiting, diarrhoea, occasional disturbances in colour vision	Use during menstruation
Oral progestogen for 21 days	32–50%[26]	Bloating, fluid retention, breast tenderness, weight gain, nausea, dizziness, headache, depression, acne, rash, hirsutism, alopecia	Cycle regularisation, endometrial protection in anovular bleeding
LNG-IUS	74–97%[27,28]	Intermenstrual bleeding in first three cycles. Other adverse effects similar to progestogens	Contraceptive agent, endometrial protection
Long-acting progestogen	50–66%[29] of patients experience amenorrhoea between 1–2 years of use	Menstrual irregularity, weight gain, vaginal dryness, reduced libido, mood changes	Contraceptive agent
Combined oral contraceptive	43%[30]	Nausea, vomiting, headache, breast tenderness, break-through bleeding, weight gain	Contraceptive agent, cycle regulation, improves dysmenorrhoea, and premenstrual syndrome. Reduces the risk of pelvic inflammatory disease, ovarian and endometrial cancer and benign breast disease
Danazol	49.7%[16]	Muscle cramps, fatigue, weight gain, fluid retention, breast atrophy, acne, oily skin, hirsutism, atrophic vaginitis	Improves dysmenorrhoea
GnRH analogues	>90%[31]	Hot flushes, night sweats, vaginal dryness, dyspareunia and loss of libido, bone loss	Improves dysmenorrhoea and severe premenstrual symptoms

GnRH = gonadotropin-releasing hormone; **LNG-IUS** = levonorgestrel-releasing intrauterine system.

therapy, randomised trial, clinical trial, systematic review, NSAIDs, nonsteroidal anti inflammatory agents, mefenamic acid, naproxen, flurbiprofen, antifibrinolytics – tranexamic acid, cyclokapron, etamsylate, progestogens, cyclical progestogens, norethisterone, norethindrone, medroxy progesterone acetate, long acting progestogens, contraception, medicated intrauterine devices, progestogen releasing intrauterine system, levonorgestrel releasing intrauterine system, oral contraceptive pills, danazol, gestrinone, gonadotrophin releasing hormone analogues, LHRH analogues.

1. NSAIDs

NSAIDS have been widely used over the past 2 decades for the treatment of menorrhagia.

NSAIDs inhibit the cyclooxygenase (COX) enzyme system responsible for the conversion of arachidonic acid to cyclic endoperoxidases (prostaglandins and leukotrienes).[18] Some NSAIDs (mefenamic acid, meclofenamic acid) are also believed to act by binding with the receptor of the vasodilator prostaglandin E_2.[19]

The NSAIDs used for the treatment of menorrhagia include mefenamic acid, naproxen, ibuprofen, flurbiprofen, meclofenamic acid, diclofenac, indomethacin and aspirin (acetylsalicylic acid). Of these, mefenamic acid is the most frequently prescribed preparation. It is usually assumed that there are no differences in clinical efficacy between the different NSAIDs although idiosyncratic variations in individual responses are known to occur. NSAIDs have been shown to reduce menstrual blood loss by 20–50% in three-quarters of women with menorrhagia (table II).[20] The response may sometimes be even greater, reaching up to an 80% reduction, and is directly proportional to the volume of pretreatment loss.[21,22] Treatment with mefenamic acid is effective in patients with menorrhagia associated with adenomyosis, intrauterine contraceptive devices (IUCD) and coagulopathy[21,23] and the effect is sustained for the duration of treatment.[24]

Lethaby et al.[32] reviewed 16 randomised controlled trials of individual NSAIDs comparing their

efficacy with either placebo, other NSAIDs, or alternative drugs in women with dysfunctional uterine bleeding. In five out of seven trials that compared NSAIDs with placebo, NSAIDs significantly reduced menstrual blood loss and led to relief of menstrual symptoms.[32] Small trials comparing NSAIDs with etamsylate,[33] oral luteal progestogens,[34,35] progesterone impregnated coil[35] and the oral contraceptive pill[30] have failed to show significant differences in terms of reducing menstrual blood loss. The data suggest a trend towards a lower menstrual blood loss with mefenamic acid when compared with either etamsylate or oral progestogens. Tranexamic acid (trans-4-aminomethylcyclohexanocarboxylic acid) and danazol were both more effective than NSAIDs in reducing menstrual blood loss[32] (table III). Compared with NSAIDs, the length of the bleeding phase was significantly longer with the progesterone-impregnated coil[35] and significantly shorter with danazol.[36] These data should be interpreted with caution as they are based on small sample sizes.

The fact that NSAIDs only need to be used during the menstrual phase has obvious advantages in terms of patient compliance and adverse effects. Their analgesic property is particularly useful in women with concomitant dysmenorrhoea,[22,36] and menstrual migraine.

The adverse effects of NSAIDs vary in severity and frequency according to the nature and dose of the actual preparation. Abdominal discomfort, nausea, diarrhoea, gastrointestinal bleeding and ulceration may occur,[48] headache, dizziness, rashes, hypersensitivity reactions, and rarely blood disorders like haemolytic anaemia or thrombocytopenia have also been reported.[48] The proportion of women experiencing adverse effects while taking NSAIDs for menorrhagia has been reported to be between <10 and 59%.[25] The incidence of serious adverse effects were not significantly different between mefenamic acid and naproxen, however, gastrointestinal adverse effects were fewer with mefenamic acid.[38] A randomised controlled trial comparing mefenamic acid and danazol[36] showed a higher incidence of adverse events with danazol compared with mefenamic acid. In a separate study comparing etamsylate and mefenamic acid[33] a significantly greater proportion of women found that treatment with etamsylate was unacceptable.

No data addressing the resource implications of NSAIDs are available;[32] however, in terms of direct costs, mefenamic acid is considered to be one of the most economic choices for the treatment of menorrhagia.[31]

2. Antifibrinolytics

Women with heavy menstrual bleeding have higher levels of plasminogen activators in the endometrium compared with those with normal menstrual loss.[17] Antifibrinolytic agents (plasminogen activator inhibitors) such as tranexamic acid, competitively inhibit the conversion of plasminogen to plasmin and counteract the fibrinolytic activity within the endometrium.

Tranexamic acid and its precursors are believed to be the only true inhibitors of plasminogen activators that are currently used for the treatment of menorrhagia. Epsilon amino caproic acid (etamsylate), which was thought to have a similar action to that of tranexamic acid is now known to reduce capillary bleeding by correcting abnormal platelet function.[17]

Previous studies using tranexamic acid for the treatment of menorrhagia have consistently reported a 47–54% reduction in menstrual blood loss.[25] In a recent meta-analysis, Coulter et al.[16] found that tranexamic acid reduced mean menstrual blood loss by 46.7% (95% CI 45.0–46.7%). The precursor of tranexamic acid, Kabi 2161, has also been used for treatment of menorrhagia. This is rapidly converted to the active drug and has the advantage of better gastrointestinal absorption and increased bioavailability. In a randomised controlled trial, the use of this prodrug reduced menstrual blood loss by 33–41%.[40] Tranexamic acid also improves heavy menstrual loss associated with the use of IUCDs.[31]

Lethaby et al.[17] conducted a review of trials comparing the use of antifibrinolytic agents with either placebo, no treatment or other medical treatments for cyclical heavy menstrual bleeding. Two trials comparing antifibrinolytic therapy with placebo,[40,41] showed a significant reduction in mean blood loss in the treatment group (weighted mean difference –94.0mL (95% CI –151.4mL to

Table III. Trials performing direct comparisons of pharmacological agents for the treatment of menorrhagia

Drug compared	Reduction in menstrual blood loss (objective/subjective assessment)	Additional results	Adverse effects
NSAIDs			
NSAIDs vs placebo	Significantly better with NSAIDs (objective and subjective)[32]	Relief of symptoms better with NSAIDs[37]	No difference
Mefenamic acid vs naproxen[38]	No difference	NA	Fewer gastrointestinal adverse effects with mefenamic acid
NSAIDs vs tranexamic acid[32]	Significantly better with tranexamic acid (objective and subjective)	No significant difference in relief of symptoms	NA
NSAIDs vs danazol[32]	Significantly better with danazol (objective and subjective)	Duration of menses less with danazol	Fewer adverse effects with mefenamic acid
NSAIDs vs COCP[32]	No difference	NA	NA
Mefanamic acid vs etamsylate[39]	Significantly better with mefenamic acid (objective and subjective)	No difference in duration of menses	Gastrointestinal adverse effects higher with mefenamic acid
Tranexamic acid			
Tranexamic acid vs placebo[40,41]	Significantly better with tranexamic acid (both objective and subjective)	Relief of symptoms marginally better with tranexamic acid	No difference
Tranexamic acid vs luteal phase oral progesterone[42]	Significantly better with tranexamic acid (objective)	Relief of symptoms better with tranexamic acid	No difference
Tranexamic acid vs etamsylate[39]	Significantly better with tranexamic acid (both objective and subjective)	Trend of relief of symptoms in favour of tranexamic acid	No difference
Progestogens			
Luteal phase progestogen vs danazol[43]	Significantly better with danazol (both objective and subjective)	Shorter duration of menses with danazol	Increased with danazol
Luteal phase progestogen vs mefenamic acid[43]	No significant difference (objective)	No difference in duration of menses	No difference
Luteal phase progestogen vs Progestasert®a[43]	Significantly better with Progestasert® (objective)	Longer duration of menses with Progestasert®	No difference
LNG-IUS			
LNG-IUS vs flurbiprofen[44]	Significantly better with LNG-IUS (objective)	NA	No difference
LNG-IUS vs tranexamic acid[44]	Significantly better with LNG-IUS (objective)	NA	No difference
LNG-IUS vs norethisterone (days 5–26)[45]	No significant difference with LNG-IUS (objective)	Greater patient satisfaction with LNG-IUS; no difference in QOL (qualitative outcome)	Less intermenstrual bleeding and breast tenderness with norethisterone
LNG-IUS vs TCRE[46,47]	Significantly better with TCRE (subjective)	No significant difference in patient satisfaction or QOL (qualitative outcome)	Higher incidence of adverse events with LNG-IUS

a The use of tradenames is for product identification purposes only and does not imply endorsement.

COCP = combined oral contraceptive pill; **LNG-IUS** = levonorgestrel-releasing intrauterine system; **NA** = not assessed; **QOL** = quality of life; **TCRE** = transcervical resection of the endometrium.

–36.5mL). The only study[40] to evaluate women's perceptions of menstrual loss found no difference between the two groups.

A single trial comparing tranexamic acid with oral luteal phase progestogen therapy[42] demonstrated a reduction in menstrual blood loss accompanied by an improvement in quality of life in women taking tranexamic acid. In other studies comparing tranexamic acid with NSAIDs, the reduction in menstrual blood loss with tranexamic acid was greatest (53–54%) than either flurbiprofen (24%)[49] or mefenamic acid (20%).[39] However, this difference was not reflected in women's assessments of their menstrual symptoms.[39]

The only study comparing tranexamic acid with etamsylate[39] showed a marked reduction in objec-

tively measured menstrual blood loss in patients receiving tranexamic acid group after 3 months of treatment. No difference was noted in the duration of menstruation, but the women taking tranexamic acid used significantly fewer sanitary pads.

Similar to NSAIDs, tranexamic acid needs to be taken only for the duration of menses. This is preferable to long-term daily medication in terms of adverse effects. Until very recently, tranexamic acid accounted for <5% of the treatments prescribed by general practitioners for patients with heavy menstrual bleeding.[50] The reluctance to prescribe antifibrinolytics could have been due to concern about possible adverse effects, particularly thrombogenic events, as tranexamic acid is contraindicated in patients with thromboembolic disease. However, long-term studies in Sweden[51] have shown that the rate of incidence of thrombosis in women treated with tranexamic acid is similar to that in the general population of women. The other reported adverse effects are mainly gastrointestinal (nausea, vomiting, diarrhoea) and occasional disturbances in colour vision. A recent systematic review[17] did not find a higher incidence of adverse effects associated with antifibrinolytic treatment.

The Royal College of Obstetricians and Gynaecologists recommends tranexamic acid and mefenamic acid as first-line drugs for women with menorrhagia who either do not require contraception or prefer non-hormonal treatment.[52] A randomised controlled trial carried out in primary care in East Anglia (UK), showed that the use of tranexamic acid for menorrhagia varied between 57% in practices given a specific evidence-based education package and 35% among controls.[53] Although the average daily cost of tranexamic acid is more than that of mefenamic acid (£1.42 vs £0.24 [2002 values]),[54] the total cost of treatment as an outcome measure has not been evaluated by any of the trials of antifibrinolytic therapy.[17]

3. Etamsylate

Etamsylate is a haemostatic agent, which corrects abnormal platelet function and reduces bleeding by maintaining capillary integrity.[17] It also inhibits the prostaglandin pathway[55] but appears to act at a different enzymatic point from other NSAIDs.[56]

Studies evaluating the use of etamsylate in menorrhagia have reported variable levels of efficacy of the drug. A double-blind trial,[57] found a significant reduction in the duration of bleeding and the number of tampons (20%) used in women receiving etamsylate compared with placebo. In another early study, the use of etamsylate was associated with a 50% reduction in menstrual blood loss in women with primary menorrhagia and a 19% reduction in menstrual blood loss in women with menorrhagia due to an IUCD.[58]

More recent randomised controlled trials[33,39] comparing etamsylate with other medical treatments (mefenamic acid, tranexamic acid), have failed to demonstrate any significant clinical advantages of this drug. In a comparison trial with mefenamic acid,[33] the overall reduction in menstrual blood loss was 20% in the etamsylate group and 24% in the mefenamic acid group. Blood loss was lower in each of the 3 treatment months for women receiving mefenamic acid, but was lower only in the second and third months of treatment for women receiving etamsylate. A randomised controlled trial comparing all three non-hormonal medical treatments (etamsylate, mefenamic acid and tranexamic acid)[39] failed to demonstrate a reduction of mean menstrual blood loss with etamsylate, although mefenamic acid and tranexamic acid reduced blood loss by 20% and 54%, respectively.

Similar to other non-hormonal treatments of menorrhagia, etamsylate is administered only during menstruation. Occasional adverse effects include nausea, headache and rashes. Although the literature does not show any difference in the frequency and severity of adverse effects compared with other medical treatments, etamsylate, is no longer considered an effective treatment of menorrhagia because of its limited efficacy.[52]

4. Progestogens

4.1 Cyclical Progestogens

Although a majority of patients with heavy menstrual loss have ovulatory dysfunctional uterine bleeding,[9,59] cyclical progestogen has been a popular treatment for menorrhagia, particularly in primary care. In particular, oral luteal phase norethister-

one has been, until recently, a commonly prescribed drug. Progestogens (norethisterone, dydrogesterone, medroxyprogesterone) in total made up 55% of prescriptions for the treatment of menorrhagia by general practitioners in the UK.[16]

Progestogens can be used cyclically in two different treatment protocols – a short course during the luteal phase, and a relatively longer course lasting 21 days from day 5 of the cycle. A meta-analysis of four randomised controlled trials failed to show a reduction in menstrual blood loss with norethisterone 5mg two to three times a day in the luteal phase of the cycle.[16] The results actually show an increase in menstrual blood loss in women using norethisterone with the combined percentage reduction of menstrual blood loss calculated as –3.6%. However, in a single non-randomised study, the use of norethisterone 10mg three times a day for 21 days (day 5–25) reduced menstrual blood loss in both anovulatory (50% reduction) and ovulatory (32–36% reduction) cycles.[26]

In a recent systematic review of oral progestogen therapy[43] (taken either during the luteal phase or for a longer duration of 21 days) intended to include trials that compared oral progestogen therapy either with placebo or other drugs for the treatment of menorrhagia. Seven randomised controlled trials were included in the review. However no trial comparing oral progestogens with placebo was available to include in this review. Norethisterone was the only type of progestogen that was assessed in all of the trials.

Six small randomised controlled trials, with a total of 252 patients with menorrhagia, compared the effects of luteal phase oral progestogen therapy (norethisterone) with danazol (three trials),[60-62] mefenamic acid (one trial),[34] tranexamic acid (one trial)[42] and danazol, mefenamic acid and a progestogen-releasing intrauterine system (Progestasert®[1]) [one trial].[35] Luteal phase progestogen therapy was less effective in reducing objectively measured mean menstrual blood loss when compared with either danazol, tranexamic acid or Progestasert® (table III). Furthermore, in terms of the patients' subjective assessment, luteal phase norethisterone therapy was associated with a significantly higher perceived blood loss than danazol.[62] Data from the trial comparing mefenamic acid and luteal phase norethisterone therapy[34] favoured the former although the results did not reach statistical significance because of the small number of cases.

A single trial comparing cyclical norethisterone therapy (norethisterone 5mg daily from days 5–26 of the cycle) with the levonorgestrel-releasing intrauterine system (LNG-IUS)[45] showed a significant reduction in menstrual blood loss in both groups, although this was more marked with LNG-IUS.

The adverse effects of progestogens include premenstrual-like syndrome (bloating, fluid retention, breast tenderness), weight gain, nausea, dizziness, headache, insomnia, drowsiness, depression, skin reactions (acne, rash), hirsutism and alopecia.[63] Jaundice and anaphylactoid reactions have been occasionally reported.[63] The prolonged use of high-dose progestogens is sometimes associated with irregular bleeding and atherogenic changes in the lipid profile.[43]

The number of adverse effects associated with luteal phase norethisterone are similar to those caused by mefenamic acid and tranexamic acid,[43] and fewer than those associated with danazol (table III).[60,62] The use of tranexamic acid has been associated with improved quality of life measures (flooding, leakage and sexual function) compared with luteal norethisterone.[42]

Women receiving the long oral regimen of norethisterone (during days 5–26) experienced a lower incidence of intermenstrual bleeding and breast tenderness than women receiving LNG-IUS.[45] Despite this, more women in the LNG-IUS group found their treatment acceptable. There was little difference between the two groups in terms of quality of life. Cost effectiveness of oral progestogen therapy was not assessed in any of the trials mentioned above in this section.

In summary, luteal phase oral progestogen therapy has not been found to be superior to other medical treatments (NSAIDs, tranexamic acid, danazol) for the treatment of menorrhagia. A 21-day regimen of oral progestogen therapy results in a significant reduction of menstrual blood loss and

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

may have a role in the short-term treatment of menorrhagia.

4.2 Progestogen-Releasing Intrauterine Systems

Progestogenic compounds (progestogens) stabilise the endometrium by inducing secretory changes, and are effective in treating heavy menstrual blood loss if released directly within the uterine cavity.

Progestogen-impregnated IUCDs, such as Progestasert®, have been known to reduce menstrual blood loss in women with menorrhagia.[64] In a small trial comparing Progestasert® with other medical treatments for menorrhagia (mefenamic acid, danazol and oral luteal phase norethisterone),[35] Progestasert® reduced menstrual blood loss and was possibly more effective than luteal-phase norethisterone in this context. Progestasert® did not appear to be superior to either mefenamic acid or danazol, and later had to be withdrawn as a contraceptive device because of an increased risk of ectopic pregnancy.[65]

The LNG-IUS was developed in the mid-1970s in Finland. The aim was to achieve better contraceptive efficacy with fewer adverse effects (such as menorrhagia) than copper IUCDs. Originally, LNG-IUS was licenced for contraceptive use for a maximum of 3 years, however, in 1998 the period of use was extended to 5 years. The current version of LNG-IUS consists of a plastic T-shaped device with a steroid reservoir in the vertical stem which releases levonorgestrel 20μg per 24 hours within the uterine cavity at a steady rate for at least 7 years. Most of the released levonorgestrel is absorbed in the basal layers of the endometrium. A small amount reaches the systemic circulation and plasma progestogen levels are lower than those associated with other hormonal contraceptives.[65] It is an effective reversible contraceptive, which does not suppress ovulation and is associated with expulsion rates that are comparable to other intrauterine devices.[27]

Several clinical studies have demonstrated significant reductions (≥90%) in menstrual blood loss with LNG-IUS,[27,28] with relatively few adverse effects,[66] in women with menorrhagia. Six studies have reported improvements in haemoglobin levels ranging from 8.0 to 19.2%, while four studies have confirmed elevations in serum ferritin levels[27] in women treated with LNG-IUS. LNG-IUS is associated with impressive levels of efficacy and, unlike surgical treatment, it preserves fertility. Although it is a relatively new intervention, these factors have facilitated its current role as a favoured treatment for menorrhagia.

Lethaby et al.[28] performed a systematic review of progestogen-releasing intrauterine devices for the treatment of menorrhagia. Five randomised controlled trials were identified. One study used Progestasert®[35] and four compared the use of LNG-IUS (releasing levonorgestrel 20μg in 24 hours) with other medical or surgical treatments.[44-46,67] Stewart et al.[27] also systematically reviewed the efficacy of LNG-IUS for treating menorrhagia. Their review included five randomised controlled trials (in a total of 110 women with menorrhagia) and five case series (involving a total of 101 women with menorrhagia). Both systematic reviews concluded that LNG-IUS significantly reduced menstrual blood loss in women with confirmed menorrhagia. Although LNG-IUS has not been compared with placebo or 'no treatment' control groups, women treated with LNG-IUS have been shown to achieve an average of 90% (74–97%) reduction in menstrual blood loss from baseline values.[27,28]

The reduction in mean menstrual blood loss at 12 months with LNG-IUS (96%) was significantly greater than that with either flurbiprofen (21%) or tranexamic acid (44%).[44] In a randomised trial comparing LNG-IUS with oral norethisterone (given during days 5–26 of the cycle),[45] the median reduction of menstrual blood loss was 85% at the end of 1 month and 94% at the end of 3 months in the LNG-IUS group compared with 62% after 1 month and 83% after 3 months in the norethisterone group. However, this difference was not statistically significant. But a greater proportion of women had amenorrhoea in the LNG-IUS group (32%) compared with norethisterone (0%). More women in the LNG-IUS group were willing to continue with their treatment in comparison with the norethisterone group (77% vs 22%). In a trial of women awaiting hysterectomy for menorrhagia, those using LNG-IUS were more likely to cancel their surgery after 6 months' treatment than those on other medical treat-

ment (64% vs 14%).[67] In another case series, 82% of women using LNG-IUS for menorrhagia were taken off the waiting list for surgery after 12 months of treatment.[68]

Two trials have compared LNG-IUS with TCRE.[46,47] In the first study[46] the reduction of mean menstrual blood loss at 6 months was significantly less in the LNG-IUS group (79%) compared with that achieved with endometrial resection (89%). However, patient satisfaction rates were similar in the two groups. The second study[47] reported a similar reduction in menstrual blood loss at 1 year (90% with LNG-IUS vs 98% with TCRE) and this trial also demonstrated a higher amenorrhoea rate at 12 months in the TCRE group.

The adverse effects associated with LNG-IUS can be divided into two groups: (i) those related to the mechanical effects of an IUCD (including irregular bleeding, cramping, dysmenorrhoea, ectopic pregnancy, pelvic infection and expulsion of device); and (ii) those related to systemic effects of progestogens (including breast tenderness, weight gain, bloating and excessive hair growth). The most commonly reported adverse effect is intermenstrual bleeding/spotting in the first three cycles. Others are weight gain, bloating, mood swings, greasy hair, depression/anxiety, hair loss, reduced libido, hypertension, leg pain and headache.[27]

Although LNG-IUS releases a small amount of levonorgestrel every day, the trial comparing LNG-IUS and oral norethisterone[45] found no difference in the incidence of progestogenic adverse effects. One of the trials comparing LNG-IUS and TCRE has reported a higher rate of adverse effects (mostly progestogenic) with LNG-IUS (table III).[46] There is no evidence of increased dysmenorrhoea in women with LNG-IUS.[28] Trials of LNG-IUS for the treatment of menorrhagia have not reported on rates of pelvic infection or ectopic pregnancy but the contraceptive studies have shown that the risk of ectopic pregnancy is considerably smaller than with other intrauterine devices.[69] Three trials have reported expulsion rates of the device within 12 months of 3.3%, 4.6% and 5.9%.[28] In a systematic review, Stewart et al.[27] found that the average treatment discontinuation rate with LNG-IUS was 20% in randomised controlled trials and 17% in case series. The rates for individual studies varied from 9% to 25%.

LNG-IUS was superior to oral norethisterone (21-day course) in terms of patient satisfaction and acceptability.[45] The percentage of women rating the treatments as 'well' or 'very well' was 64% for LNG-IUD and 44% for norethisterone. Furthermore, 77% and 22% of women elected to continue with LNG-IUS and norethisterone, respectively. The two trials that attempted to assess quality of life,[45,46] found no significant differences between LNG-IUS and other treatments (norethisterone and TCRE), and these trials were inadequately powered to show significant changes in either satisfaction or quality of life. However, women using LNG-IUS scored better on a number of different quality of life parameters such as general well being, work performance, physical activity, sex life and leisure activity compared with those on alternative medical treatments prior to scheduled hysterectomy.[67]

A more recent trial in Finland has evaluated quality of life and cost effectiveness of LNG-IUS versus hysterectomy in women with menorrhagia.[70] Using the EQ-5D[71] questionnaire, the authors showed significant improvements in health-related quality of life scores at 12 months in both groups; however, a higher pain score was noted in the LNG-IUS group. At 1 year, the total estimated cost per woman was approximately three times higher in the hysterectomy group compared with the LNG-IUD group ($US4222 vs $US1530 [2001 values]). The authors concluded that while both treatment modalities (LNG-IUS and hysterectomy) were comparable in terms of health status, health-related quality of life and psychosocial well-being (except for pain), LNG-IUS was superior to hysterectomy in terms of cost-effectiveness.

There are no data relating to the cost effectiveness of LNG-IUS compared with other medical treatments. Crude estimates can be made by extrapolating available data relating to costs. A single LNG-IUS costs £89.25[69] in the UK (2002 values). The annual cost of its use would amount to £18.00 if used for its full duration of 5 years and compares favourably with 1-year treatment cost with high-dose (21-day course) of oral norethisterone (£54.50) or tranexamic acid (£69.10) [2002 values].[54,72] This does not take into account other costs involved such

as insertion, follow-up visits, removal and counselling. Data from New Zealand suggest that LNG-IUS costs approximately $NZ5.00 a month when used for the full time span of 5 years (1998 values).[73]

A recently published follow-up of the case series originally reported by Barrington and Bowen-Simpkins[68] showed a continuation rate of 50% in women using LNG-IUS after a mean follow up of 54 months. Only 26.4% of the women in this cohort eventually needed surgical treatment,[74] failures usually occurred within 2 years of insertion of the intrauterine system. Women nearing menopause were more likely to continue with the device. In light of the evidence presented so far, it would appear that LNG-IUS is an effective method of treatment for heavy menstrual bleeding and is particularly suitable for women who require contraceptive protection and wish to preserve their fertility; but may also be considered as an alternative to surgical treatment in women who have completed their family.[75]

4.3 Long-Acting Progestogens

Long-acting progestogen injections/implants are used as contraceptives in over 100 countries.[29] Intramuscular depot medroxyprogesterone acetate (DMPA) is commonly used in a dose of 150mg every 12 weeks. This preparation is likely to cause unpredictable and irregular bleeding in the first few months of its use.[76,77] Although heavy bleeding is encountered by 1–2% of users,[78] most women experience reduced menstrual blood loss or amenorrhoea with increasing duration of use. Amenorrhoea has been reported in more than 50% of DMPA users within 1 year of insertion and in 66% of users within 2 years of insertion.[29] In addition, DMPA reduces dysmenorrhoea and improves symptoms of premenstrual dysphoric disorder.[29] Reduced menstrual blood loss or amenorrhoea eventually results in improved haemoglobin levels.[77] These attributes are often considered while offering DMPA as a treatment of heavy menstrual bleeding in women requiring contraceptive protection.

Despite the paucity of randomised controlled trials, the Royal College of Obstetricians and Gynaecologists (UK)[52] recommends the use of long-acting progestogens as a first-line drug for the management of menorrhagia in women requiring contraceptive protection. However, concerns about associated adverse effects continue to be voiced. Although DMPA has been available in the UK since 1984 as a contraceptive, <1% of women use this agent and a relatively high proportion of users (20–50%) discontinue within 1 year.[29,79,80] Irregular menstrual bleeding, weight gain, breast tenderness and depression are common causes for stopping the drug.[81,82] Menstrual irregularity, which is the most common source of dissatisfaction, results in one-quarter of all users wishing to discontinue the drug within the first 12 months.[83] Approximately 70% of users gain weight (up to 2kg) in the first year[29] and there is evidence that the weight gain is due to an accumulation of fat rather than fluid retention.[84] Vaginal dryness and reduced libido has been reported in young women.[85] Mood changes and depression[79] are also reported, although it is unclear whether these adverse effects are solely due to DMPA. Concern has been expressed about the effect of prolonged amenorrhoea and hypoestrogenism in long-term users. A small reduction of bone density has been reported in women using DMPA for more than 5 years[86] and adverse changes in the lipid profile of long-term users has been noted.[87]

Long-acting progestogen-releasing implants (Norplant®, a levonorgestrel-releasing implant and Implanon®, an etonogestrel-releasing implant) have positive effects on menstruation that are very similar to injectable DMPA and may be used for the treatment of menorrhagia in women requiring contraceptive protection. However, the adverse effects of long-acting progestogen-releasing implants and DMPA are also similar,[69] and Norplant® has been discontinued in the UK.

5. The Combined Oral Contraceptive Pill

In addition to being a highly reliable method of contraception, the combined oral contraceptive pill (COCP) provides a variety of beneficial effects. Taken cyclically, it inhibits ovulation and ensures withdrawal bleeding from estrogen and progestogen primed endometrium. Under the influence of exogenously administered hormones, the endometrium shows less proliferation of the glandular epithelium and is thinner than in normal ovulatory cycles.[88] This results in a reduced blood loss at the time of endometrial shedding[88] and makes it a suitable

form of therapy for women with menorrhagia requiring contraceptive protection.[89]

Over the years there has been a progressive reduction in the estrogen component in the COCP. Few studies have evaluated the efficacy of the newer low-dose COCP for the treatment of menorrhagia. Earlier studies reported on the efficacy of high-dose preparations (containing either ethinylestradiol 50μg or mestranol 0.15mg).[90,91] In a series of 164 women with objective menorrhagia, who were administered the COCP for a total of 284 cycles, a 52.6% reduction in menstrual blood loss was achieved in 68% of patients.[91] An improvement in menstrual blood loss was proportional to pretreatment blood loss. Normalisation of menstrual blood loss was noted in 88.5% of women with pretreatment blood loss of <100 mL/cycle, compared with 69% of women with pretreatment loss between 100–200mL and 44.5% of women with pretreatment loss between 200–300mL.

Iyer et al.[89] performed a systematic review of randomised controlled trials that compared the oral contraceptive pill with other drugs, placebo or no treatment in women with regular heavy periods (measured subjectively or objectively). Only one trial met the inclusion criteria of the reviewers.[30] The trial was relatively small (45 participants) and used a crossover design. The treatments that were compared were mefenamic acid, naproxen, low-dose danazol and the combined oral contraceptive pill (ethinylestradiol 30μg and levonorgestrel 150μg). In the group randomised first to mefenamic acid and then COCP, a highly significant reduction in menstrual blood loss of 43% was obtained with COCP. This was similar to the 38% reduction of menstrual blood loss obtained with mefenamic acid. There were no differences between COCP and low-dose danazol or between COCP and naproxen in terms of menstrual blood loss. The reviewers concluded from this single study that COCP (ethinylestradiol 30μg) appeared to be effective in reducing menstrual blood loss in patients with menorrhagia. Uncontrolled data[92-95] provides supportive evidence that COCP reduces menstrual blood loss in women with normal periods as well as those with menorrhagia. The Royal College of Obstetricians and Gynaecologists (UK) recommends the use of the combined oral contraceptive pill as a first-line drug for the management of menorrhagia in women requiring contraceptive protection.[52]

The combined pill reduces the incidence of dysmenorrhoea, intermenstrual bleeding, premenstrual tension and ensures predictable withdrawal bleeding by correcting cycle irregularity. The reduction of menstrual blood loss improves haemoglobin concentration and corrects iron deficiency anaemia, and has the advantage of being suitable for long-term prescription, with the exception of women who are considered to be at risk of venous thromboembolism, arterial disease or migraine.

The combined pill should be used with caution in smokers who are over 35 years of age, women with diabetes mellitus, and in women with a high body mass index or a family history of arterial disease.[96] The recognised adverse effects of the combined oral contraceptive pill include nausea, vomiting, headache, breast tenderness, spotting and breakthrough bleeding, changes in bodyweight, fluid retention, changes in libido, depression, chorea, skin reactions, irritation in contact lens users, photosensitivity (rarely) and chloasma.[96] The more serious adverse effects include thrombosis, hypertension, impairment of liver function and hepatic tumours, and adverse effects of any severity have been noted in 30–40% of users.[25] It has been suggested that spotting and breakthrough bleeding may be improved by the use of COCPs containing relatively high doses of progestogen.[97]

6. Danazol

Danazol is an isoxazole derivative of 17α-ethinyltestosterone. It suppresses the mid-cycle surge of follicle-stimulating hormone and luteinising hormone and inhibits ovulation without altering basal gonadotropin levels in premenopausal women.[98] Danazol also inhibits steroidogenesis in the corpus luteum[99] and thereby creates a hypoestrogenic and mildly androgenic environment which results in endometrial suppression.

A number of randomised controlled trials have confirmed that danazol, in different dose schedules varying from 50–400 mg/day, is effective in reducing menstrual blood loss by 22–99% in women with menorrhagia.[30,35,36,60,62,100] Menstrual blood loss reduction seems to be related to the dosage and the

duration of treatment and danazol is more effective in the second or third cycle of treatment, compared with the first treatment cycle. Danazol 200mg once daily seems to be most acceptable in terms of efficacy, adverse effects and cycle control.[62,100,101] Lower doses cause irregular bleeding and less reduction of menstrual blood loss[100,101] whereas with higher doses (400 mg/day) amenorrhoea is common and adverse effects can be unacceptable.[102] A meta-analysis[16] of five randomised controlled trials using danazol for the treatment of menorrhagia[30,35,36,62,101] showed an overall reduction in menstrual blood loss of 49.7%.

More recently, Beaumont et al.[103] performed a systematic review of randomised controlled trials comparing danazol with placebo or other medical treatments of menorrhagia. A total of nine studies were included; the only study that compared danazol and placebo showed a significant reduction in blood loss (as assessed by a scoring system) with danazol.[104] The data from trials comparing danazol with other medical treatments showed danazol to be more effective than oral progestogens (given in luteal phase), NSAIDs (mefenamic acid, naproxen) and COCP, but was associated with an increased frequency of adverse effects.

In a study comparing mefenamic acid (500mg three times a day from day 3 to day 5 in two cycles) and danazol (100mg twice a day for 60 days),[36] a significant reduction of menstrual blood loss was achieved in both groups. Both were equally effective in improving dysmenorrhoea, but the effect of danazol on menstrual blood loss was more pronounced (60% reduction vs 20% reduction with mefenamic acid).

In a small crossover study, Fraser and McCarron[30] compared danazol 200mg once a day with an oral contraceptive (ethinylestradiol 30μg and levonorgestrel 150μg) in 12 women with menorrhagia. After 2 months of treatment, objectively measured mean menstrual blood loss in the danazol group was significantly lower than that for the oral contraceptive group.

The adverse effects of danazol are related both to the hypo-estrogenic environment it creates and to its androgenic properties. They include muscle cramps, fatigue, weight gain, fluid retention, decreased breast size, acne, oily skin, growth of facial hair, atrophic vaginitis, hot flushes, decreased libido and emotional lability.[98] Androgenic adverse effects may result in voice changes,[105] hirsutism, alteration of lipoprotein profile and other metabolic changes such as insulin resistance.[106] Clitoral hypertrophy is a rare complication.[106] No study of danazol has assessed its cost effectiveness for the treatment of menorrhagia. A relative cost (for 6 months' treatment) assessment of different medical treatments for menorrhagia showed that danazol was more expensive than the majority of other medical treatments (mefenamic acid, tranexamic acid, oral contraceptive pill and oral progestogens) but cheaper than gonadotropin-releasing hormone (GnRH) analogues.[31]

7. Gestrinone

Gestrinone is a synthetic 19-nortestosterone derivative, whose effect on menorrhagia is similar to danazol.[107] It causes anovulation by acting on the hypothalamic pituitary axis and suppressing gonadotrophin secretion; it induces amenorrhoea and endometrial atrophy and is an effective agent for the treatment of endometriosis.

The efficacy of gestrinone in reducing menstrual blood loss in women with menorrhagia has been assessed in a single-blind, placebo-controlled trial.[108] Gestrinone 2.5mg twice weekly (for five cycles) was administered to 19 patients with objectively proven menorrhagia. It reduced heavy menstrual bleeding in 15 patients (79%) whereas placebo had no effect on menstrual blood loss. In the UK, gestrinone is licensed only for use in endometriosis and is five times more expensive than danazol. The adverse effects of gestrinone (acne, fluid retention, hirsutism, voice change, change in libido, decrease in breast size) are similar to danazol.[107]

The Royal College of Obstetricians and Gynaecologists (UK) considers danazol and gestrinone to be second-line drugs for the management of menorrhagia,[75] and should be used only when first-line drug therapy has failed and intra-uterine pathology has been excluded.

8. Gonadotropin-Releasing Hormone Analogues

GnRH analogues bind to the GnRH receptors in the pituitary as competitive agonists. The prolonged exposure to GnRH analogues leads to desensitisation of GnRH-releasing cells in the anterior pituitary eventually leading to a hypogonadotropic state. This results in severe hypo-estrogenism leading to endometrial atrophy,[109] and amenorrhoea.

In a small study reported by Shaw and Fraser[110] involving four patients with menorrhagia (objectively assessed menstrual blood loss >80mL) without any pelvic pathology, intranasal buserelin for 3 months caused a temporary reduction of menstrual blood loss. Soon after stopping the treatment, menstrual blood loss returned to pretreatment levels. In another study, Shaw and Duckitt[109] investigated the efficacy of goserelin in six women with objectively proven menorrhagia. Subcutaneous goserelin 3.6mg was administered every 4 weeks for 3 months. By the second cycle, five of the six women (>90%) became amenorrhoeic and the sixth woman had a menstrual blood loss of 2mL. None of the women experienced bleeding in the third treatment cycle or the first posttreatment cycle. After 7–10 weeks of stopping the treatment, menstrual blood loss approached pretreatment values.

The adverse effects of GnRH analogues are those of estrogen deprivation, e.g. hot flushes, night sweats, vaginal dryness, dyspareunia and loss of libido,[107] and the use of GnRH analogues is also associated with a reduction in trabecular bone density. Goserelin for 6 months has been shown to precipitate a 5% loss in bone-mineral density,[111] which was partially corrected in the 6 months after discontinuation of treatment.

The adverse effects, including the effect on bone density, can be minimised by simultaneous hormone replacement (an estrogen and a progestogen or with tibolone).[107] An open observational study compared menstrual blood loss before, during and after 3 months of goserelin depot injections with simultaneous cyclical hormone replacement therapy in 20 women with subjective menorrhagia and without any pelvic pathology.[112] In women with pretreatment blood loss >80mL, the median pretreatment loss was 171mL, which was reduced to 73.5mL by the third month of treatment. There were also improvements in subjective complaints of clots, flooding, dysmenorrhoea and premenstrual symptoms after 3 months of treatment.

GnRH analogues are effective in reducing menstrual blood loss in women with menorrhagia, and like danazol and gestrinone, GnRH analogues are considered to be second-line drugs.[75] However, they can only be used to provide temporary relief in women awaiting surgery or natural menopause.

9. Conclusion

Menorrhagia affects the lives of many women. The assessment of severity is open to personal interpretation and objective assessment of menstrual blood loss is impractical. In treating menorrhagia, the primary aim should be to improve quality of life and many women are willing to undergo quite invasive treatment in order to achieve this. To a great extent, the demand for treatment is based on psychosocial rather than purely medical grounds[113] and there is a need to individualise the method used. The contraceptive needs and future reproductive intentions of women play an important role in determining the appropriate therapy, and at all times, women should be encouraged to participate actively in the decision-making process.[52]

Although a number of conservative and radical surgical options are available to women troubled by heavy menstrual bleeding, drug therapy remains the initial treatment of choice, and for those women who wish to preserve their reproductive function or to avoid surgery, it is the only option. In the past, the success of medical treatment of menorrhagia has been undermined by inappropriate use of drugs.[52] A lack of an evidence-based approach, problems of compliance and the presence of adverse effects have contributed to relatively poor satisfaction rates associated with medical treatment in comparison with endometrial ablation.[14] Tranexamic acid and mefenamic acid are effective first-line drugs. Despite being used extensively in the past, oral luteal phase norethisterone is probably one of the least effective agents. Women requiring contraception have the choice of the COCP, LNG-IUS or long-acting progestogens. Danazol, gestrinone and GnRH analogues are all effective in terms of reducing menstrual blood loss, but adverse effects and costs limit

their long-term use. These treatments may have a role as second-line drugs for a short period of time in women awaiting surgery.

The current evidence suggests that the LNG-IUS is an effective treatment, which preserves future fertility,[27] and further evaluation, including long-term follow up, is awaited. Meanwhile, the quest continues for the ideal form of medical treatment for menorrhagia – one that is effective, affordable and acceptable to women.

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