Review

Nonsurgical treatment options for heavy menstrual bleeding*

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Abstract

Treatment options for heavy menstrual bleeding depend on the uterine anatomy, the women's preferences and personal ideas, her age and her future child wish. If the uterus has a normal anatomy, treatment options include hormonal or non-hormonal drugs (including levonorgestrel releasing intra-uterine systems; LNG-IUS), endometrial ablation and hysterectomy. In general, the main advantage of pharmacological treatment is the reversibility and therefore the eligibility for women, independent of age and future child-wish. This article provides a literature review on the effectiveness of medical treatment (hormonal and non-hormonal) for heavy menstrual bleeding and to discuss the dilemmas experienced by women and doctors. A literature search was performed focusing on the effectiveness of hormonal and non-hormonal medical treatment of women suffering from heavy menstrual bleeding. For nonsteroidal anti-inflammatory drugs (NSAIDs) as well as tranexamic acid, direct evidence for comparison to placebo is available, for the other agents (oral progestins (luteal phase and long term); LNG-IUS; combined hormonal contraceptives (combined oral contraceptive pills, combined vaginal ring), evidence could be extracted from a recent network meta-analysis. Evidence on treatment effects on HMB of the progesterone only pill and the etonogestrel subdermal implant is lacking. LNG-IUS appears to be the best pharmacological treatment option for HMB in terms of reducing blood loss as well as improving symptoms. Professionals should be aware that a number of women want to avoid a hormone-containing treatment, this may be due to (expected) negative side effects. In conclusion, considering pharmacological treatment of HMB without underlying pathology, LNG-IUS seems to be the best option to reduce menstrual blood loss. However, it is advised to carefully listen what women want, think and believe and to make a shared tailor-made decision. Pharmacological treatment for HMB should be initiated as a surgical intervention can be avoided. However, women who are not receptive to first-line drug treatments should be given the opportunity to improve their quality of life by getting rid of disabling symptoms of heavy menstrual bleeding, by offering treatment with endometrial ablation or hysterectomy.

Introduction

Heavy menstrual bleeding (HMB) is excessive menstrual bleeding with a negative impact on a woman's life (NICE, 2018; Matteson Clark et al, 2010). Around 30% of women suffer from HMB at some time during their reproductive years making it a common reason for gynaecological consultations in both primary and secondary care (NICE, 2018; Fraser et al., 2015). Traditionally, HMB is objectively measured as blood loss of more than 80 mL per cycle (Hallberg et al., 1996). It is uncertain if women can judge their blood loss objectively enough. However, over time it seems that a woman's perception of blood loss seems to correlate with the objective amount of bleeding (Warner et al., 2004). Therefore, in clinical practice women's perception of their symptoms often leads to diagnosing and treating HMB. It is important to offer women an effective and tailor-made treatment for HMB. In order to make a well-informed and shared treatment decision, women's preferences, treatment effectiveness and differences in treatment characteristics must be considered.

The endometrium is a dynamic tissue regulated by ovarian steroid hormones, mainly oestrogen and progesterone (Jabbour et al., 2006). In response to fluctuations of the ovarian steroid concentrations, the endometrium undergoes cycles of proliferation, differentiation and breakdown of the superficial stratum functionalis (Henriet et al., 2012). This process leads to the monthly bleeding, the so-called menstrual period. Any process interfering with a part of the female reproductive tract can cause HMB (Hapangama Bulmer et al., 2016; Wouk Helton et al., 2019). According to the FIGO classification system, there are nine main categories which can cause abnormal uterine bleeding (Munro et al., 2011). These categories are arranged according to the acronym PALM-COEIN: polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; not yet classified (Munro et al., 2011). The components of the PALM group are structural aetiologies which can be assessed with imaging techniques or histopathology. The COEIN group is related to non-structural aetiologies. In women with HMB, uterine fibroids and polyps are the most common pathology found. However, in the majority of women no underlying pathology is diagnosed (NICE, 2018). The options of treatment will depend on the anatomy of the uterus, women's preferences and her personal ideas, her age and her wish to conceive in future. In case of normal anatomy of the uterus, treatment options involve hormonal or non-hormonal drugs (including levonorgestrel releasing intra-uterine systems; LNG-IUS), endometrial ablation and hysterectomy. Hysterectomy seems to be most cost-effective treatment (Roberts et al., 2011; Spencer et al., 2017). Moreover, treatment of HMB starting with LNG-IUS seems to be cheaper but slightly less effective than endometrial ablation (van den Brink et al., 2021).

In this article we focus on pharmacological treatments to reduce menstrual bleeding. In general, the main advantage of pharmacological treatment is the reversibility and therefore the eligibility for women, independent of age and future child-wish. However, women seem to become more critical to take hormones for cycle regulation (van den Brink et al., 2018). From this perspective, following the scientific results of non-surgical treatment for HMB, the dilemmas experienced by women and doctors will be discussed.

Pharmacological treatment of HMB

In women without underlying pathology pharmacological treatment can be initiated both in general and gynaecological practices. Pharmacological treatments include non-hormonal therapies; tranexamic acid (TxA) or non-steroidal anti-inflammatory drugs (NSAIDs), and hormonal therapies: progestogens, the LNG-IUS and combined oral contraceptive pills (COCP).

Tranexamic Acid (TxA), Antifibrinolytics

When bleeding occurs somewhere in the body, a network of fibrin filaments is temporarily formed, creating a blood clot and stopping the bleeding. During fibrinolysis these fibrin filaments are broken down again. TxA is an antifibrinolytic agent and reversibly blocks lysine-binding sites on plasminogen molecules. Conversion of plasminogen to plasmin is inhibited, making a blood clot less likely to dissolve. The fibrinolytic activity of menstrual blood appears to be significantly higher than that of peripheral blood. Moreover, fibrinolytic activity is even higher in the menstrual blood of patients with HMB compared with the control subjects.

Non-steroidal anti-inflammatory drugs (NSAIDs)

The precise mechanism by which excessive blood loss occurs remains speculative, especially in women without underlying pathology diagnosed. Willman et al showed higher levels of prostaglandin E2 and prostaglandin F2a in the endometrium of women with excessive menstrual bleeding when compared with women with normal menses (Willman et al., 1976). NSAIDs reduce prostaglandin levels by inhibiting the cyclo-oxygenase enzymes and therefore NSAIDs are known to reduce menstrual blood loss.

Progestogens

In the human menstrual cycle, progesterone activity plays a major role in the secretory phase. Progesterone is produced by the corpus luteum and is required for the establishment and maintenance of a pregnancy. After 10-14 days regression of the corpus luteum occurs and consequently the level of progesterone diminishes sharply. The progesterone withdrawal induces the breakdown of the functional layer of the endometrium, resulting in a bleeding which we call the menstruation. In case of anovulatory cycles, the oestrogen dominated endometrium is not organised by progesterone (as a corpus luteum is lacking) and prolonged uncontrolled bleeding can happen. In such emergency cases, administering (oral) progestins will help to stop heavy uterine bleedings. Moreover, progesterone has a strong anti-inflammatory effect and therefore could help to control HMB. The term 'progesterone' refers to the natural hormone, whereas 'progestin' refers to a synthetic product; and 'progestogens' include both kinds, the natural hormone as well as the synthetic

products. Progestins are divided in four generations, pointing to the timing of introduction. Their progestogenic effects, androgenic and oestrogenic effects differ.
Progestin therapy for HMB can be divided in cyclical therapy (during the luteal phase only) and long cycle progestins (three to four weeks regimes).

The leading progesterone only pill (POP) on the European market is desogestrel which is administered in a dose of 75mcg each day, continuously (Benagiano Primiero, 2008). Desogestrel is a third-generation progestin and it is often prescribed during breastfeeding period due to the relative contraindication for oestrogens during breastfeeding. Another advantage of POPs is the favourable cardiovascular profile compared to combined contraceptive pills. However, irregular bleeding may occur, which may be a reason for women to stop taking POPs (Hooper et al., 2010).
Etonogestrel subdermal implant(ESI) is a safe long-acting reversible contraceptive during at least three years. Etonogestrel is an active metabolite of the third generation progestin desogestrel. Like all progestogens, also etonogestrel induces endometrial changes, and therefore changes bleeding patterns (Mansour et al., 2008; Funk et al., 2005).

LNG-IUS

Levonorgestrel-releasing intrauterine system 52 mg (LNG-IUS, Mirena®, Bayer HealthCare Pharmaceuticals, Germany or Levosert®, Gedeon Richter, Budapest, Hungary) is a hormonal contraceptive and is proven as an effective treatment for HMB (Health Quality Ontario 2016). The LNG-IUS decreases menstrual bleeding by the local release of levonorgestrel which suppresses endometrial growth, by which it effectively reduces menstrual blood loss and increases quality of life (Lethaby et al., 2015). Advantages of the LNG-IUS are the contraceptive effect, the reversibility and the possibility to be inserted by both the general practitioner and the gynaecologist. Despite the general efficacy and advantages, around 40% of women discontinue the LNG-IUS within two years (Beelen et al., 2021). The discontinuation is mostly because of a lack of effectiveness, irregular bleeding, abdominal pain, or progestogenic side effects (Beelen et al., 2021).

Combined hormonal contraceptives

Combined hormonal contraceptive methods contain oestrogen and progestin. Several schedules and routes of delivery are available, including oral, vaginal, transdermal and intramuscular. Not all routes of delivery have been assessed for the treatment of HMB, only the combined oral contraceptive pill (COCP) and the combined vaginal ring (CVR) (Lethaby et al., 2019). Combined hormonal contraceptives have been associated with a higher risk of thrombotic adverse events, although the oestrogen dose has been gradually reduced from 150 μg in the original preparations to 30 μg or less, significantly reducing the risk. The combined hormonal contraceptives are now only associated with a small increased risk of venous thromboembolism (De Bastos et al., 2014). Oestrogen provides negative feedback on follicle-stimulating hormone secretion and prevents the development of a dominant follicle (Bradley Guye., 2016), providing endometrial stability and growth, improving the progestational impact. At the same time, progestin impedes the rise of luteinising hormone and consequently prevents ovulation and creates an atrophic endometrial lining. This combination reduces overall menstrual blood loss. So, combined hormonal contraceptives have two beneficial effects, inducing a regular shedding of a thinner endometrium and inhibiting ovulation, thus having the effect of both treating HMB and providing contraception.

Effectiveness of pharmacological treatment options

All these medical treatment options have recently been evaluated in an extensive network meta-analysis based on Cochrane reviews evaluating first- and second line interventions for HMB (Bofill Rodriguez et al., 2022). Primary outcomes in this review are menstrual bleeding and satisfaction. Firstline treatment options are compared to placebo as well as compared to each other. For NSAID's as well as TxA, direct evidence for comparison to placebo is available, for the other agents (oral progestins (luteal phase and long term); LNG-IUS; combined hormonal contraceptives (COCP, CVR), evidence is extracted just from the network meta-analysis. The POP as well as the ESI are excluded from the meta-analysis network, however included in this review.

Comparison to placebo

Antifibrinolytics (TxA), NSAIDs, long cycle progestogens and LNG-IUS appeared to be linked to a decrease in average blood loss in comparison to placebo. See Table I (Bofill Rodriquez et al., 2022). Certainty of evidence was moderate to very low. For the POP (desogestrel) and the ESI, data on treatment effect in case of HMB appeared to be lacking.

Table II shows results for women's perception of heavy menstrual bleeding improvement (Bofill

Table I. — Reduction in menstrual blood loss with drug treatments compared to placebo.

	Mean difference of blood loss compared to placebo (ml per cycle)	95% CI
TxA	-80,32	-127,67 to -32,98
NSAIDs	-40,67	- 84,61 to 3,27
POP	NA	NA
Cyclic progesterone(luteal phase)	-19,1	- 87,81 to 49,61
Long cycle progesterone	-76,93	- 153,82 to -0.05
ESI	NA	NA
LNG-IUS	-105,71	-201,1 to -10,3
COCP	-56,08	-140,88 to 14,50
CVR	-81,53	-177,56 to 14,50

TxA: Tranexamic acid, NSAIDs: Nonsteroidal anti-inflammatory drugs, POP: Progesterone only pill, ESI: Etonogestrel subdermal implant, LNG-IUS: Levonorgestrel-Intrauterine system, COCP: Combined oral contraceptive pill, CVR: Combined vaginal ring, NA: Not available.

Rodriquez et al., 2022). TxA, NSAID's, LNG-IUS and COCPs appeared to improve women's perception of treatment in comparison to placebo.

Comparison to other treatment options

The network meta-analysis of Bofill Rodriquez et al. (Bofill Rodriquez et al., 2022) also presents the surface under the cumulative ranking curve (SUCRA), enabling comparison of several treatment options to each other. SUCRA is a numeric representation of the overall ranking. It has a single number associated with each treatment, and the values range from 0% to 100% (Bofill Rodriquez et al., 2022). The larger the SUCRA, the higher the chances a treatment is ranked highest among all the available treatments. On the contrary, the lower the SUCRA, the more likely the intervention is to be ranked near the bottom.

The best treatment for reducing menstrual bleeding was LNG-IUS (SUCRA 100%), second long-cycle progestogen (SUCRA 80%) and third, TxA (SUCRA 80%).

The best HMB treatment in terms of perception of improvement was LNG-IUS (SUCRA 80%), second best was danazol (SUCRA 70%) and on rank three, CVR (SUCRA 70%). On rank four and five they found TxA (SUCRA 70%) and NSAIDs (SUCRA 50%). The lowest ranking is for long-cycle progestogens (SUCRA 50%), COCP (SUCRA 40%) and luteal progestogen. Nowadays, danazol is not used anymore to reduce HMB because of the side-effects.

In conclusion, both from a perspective of reduction of blood loss and from a perspective of perception of improvement of symptoms, the LNG-IUS appears to be the best pharmacological treatment option for HMB. In line with this conclusion, the NICE guideline recommends LNG-IUS as first line treatment for women suffering from HMB without underlying pathology, or the use of other medical treatments if LNG-IUS is declined or not suitable (TxA, NSAIDs, combined hormonal contraception, oral progestogens).

Patient preference

Few studies have been performed on patient preference and the treatment for HMB. Van den Brink et al. evaluated patient preference for the LNG-IUS compared to the endometrial ablation (EA) (van den Brink et al., 2018). In a discrete choice experiment, a treatment without hormones had the most influence on women's decision. Possible reasons why women want to avoid a hormone-containing treatment may be due to (expected) negative side effects (Daud Ewies, 2008). Professionals should be aware of this and inform patients about hormone-related side effects (Dutton Kai, 2023). The treatment preferences of women in primary care seem to differ from those of women referred to the gynaecologist (van den Brink et al., 2018). The general practitioner (GP) is mostly the first professional with whom women share their complaints of HMB. At this point they may have other desires and expectations regarding a treatment as compared to their later visit with the gynaecologist.

A qualitative study in primary care has been published recently interviewing women suffering

Table II. — Women's perception of heavy menstrual bleeding improvement compared to placebo.

	Relative effect (Odds ratio)	95% CI
TxA	11.13	1,79 to 69,30
NSAIDs	7.24	1,19 to 44,01
POP	NA	NA
Cyclical progestogen(luteal phase)	3,30	0,44 to 24,68
Long cycle progestogen	5,78	0,43 to 77,71
ESI	NA	NA
LNG-IUS	20,73	1,60 to 267, 83
COCP	5,43	1,19 to 24,73
CVR	14,49	0,86 to 244,30

TxA: Tranexamic acid, NSAIDs: Nonsteroidal anti-inflammatory drugs, POP: Progesterone only pill, ESI: Etonogestrel subdermal implant, LNG-IUS: Levonorgestrel-Intrauterine system, COCP: Combined oral contraceptive pill, CVR: Combined vaginal ring, NA Not available.

from HMB. Women had often normalised their menstrual blood loss which underlines the societal taboos about HMB (Cooper et al., 2023). Women (for several years) delayed seeking for help. This probably reflects the relative low knowledge about treatment options for HMB. However, if they searched for help, they could be frustrated by lack of a medical explanation for the cause of HMB. Interestingly if pathology had been diagnosed, women felt better able to understand their HMB. Experiences of medical treatment varied considerably, but were strongly influenced by interactions with doctors. Other impacts on women's treatment included considerations regarding their fertility, health concerns, family and colleagues, and views on approaching menopause (Cooper et al., 2023).

Doctor's perspective

This article evaluates first-line non-surgical treatment which is mostly initiated by the GP. Data of the Registration Network Groningen (approximately 30 000 registered patients per year) can be used to investigate how many women consult their GP with symptoms of HMB. Between 2004 and 2013 a mean annual incidence of 9.3 per 1000 person years was found, most women aged 35-54 years (van den Brink et al., 2017). Most women received hormonal treatment (46%) within three months after diagnosis, but just as large a group (44%) received no medication at all. The LNG-IUS was prescribed only in 2.4% of the women (van den Brink et al., 2017).

In the ECLIPSE primary care trial, women with HMB were randomised between LNG-IUS versus other usual medical treatments (oral TxA, mefenamic acid, combined oestrogen–progestogen; or progesterone alone) (Gupta et al., 2013). Just over 50% of participating women reported to have turned postmenopausal at long-term follow-up, however 27.2% of women reported they were using LNG-IUS at the time of response to the 10-year follow-up (Kai et al., 2016). Moreover, data of ten year follow up showed sustained low rates of progression to surgical intervention (hysterectomy (16.5%) or endometrial ablation (12.6%)). This highlights the importance and value of initiating medical management of HMB in women in primary care.

Focus for future research

A perfect treatment is not only efficacy but contains also convenience, cost, adverse effects and women's preference and choices. The definition of success for HMB has been changed to quality of life (QOL) improvement. Therefore, this should be the primary outcome of the upcoming trials and studies dealing with HMB. However, until now QOL was reported with an enormous difference in lists and outcomes. The main goal should be to worldwide agree on the same QOL-list evaluating the impact of HMB and the improvement of treatment. This highlights the importance of developing a core outcome set (COS) for heavy menstrual bleeding trials that would facilitate more effective analysis and gives the opportunity to compare or augment data of different trials. The COMET initiative (Core Outcome Measures in Effectiveness Trial) has an ongoing project, defining core outcomes for clinical trials of heavy menstrual bleeding. Recently within this project two studies have been published (Cooper et al., 2023a; Cooper et al., 2023b). The final COS for HMB should include variables that

are feasible for use in clinical trials in all resource settings and apply to the PALM-COEIN causes of the symptom of HMB. These outcomes should be reported in all future trials of interventions, their systematic reviews, and clinical guidelines (Cooper et al., 2023a). Cooper et al. concluded in their article that the COS should consists of subjective blood loss; flooding; menstrual cycle metrics; severity of dysmenorrhoea; number of days with dysmenorrhoea; quality of life; adverse events; patient satisfaction; number of patients going on to have further treatment for HMB and haemoglobin level. It would be perfect if the same lists, the same graphs, the same tables and values were used when displaying all these results.

There is also a need to investigate the advantages and disadvantages comparing first line and second line treatment options for women suffering from HMB (Bergeron et al., 2020). The endometrial ablation (EA) has been compared to the LNG-IUS in a RCT (Beelen et al., 2021), showing a cost advantage for the LNG-IUS and a satisfaction rate of 76% and 84% for LNG-IUS and EA respectively (Beelen et al., 2021; van den Brink et al., 2021). In the end 24% of the women with an LNG-IUS after two years of follow-up had a reintervention, with a hysterectomy rate of 7% for the LNG-IUS group and 10% after EA (Beelen et al., 2021). However, the outcome of the EA can probably be improved by adding directly after ablation an LNG-IUS. A systematic review evaluating this combination shows a favourable outcome for the EA plus LNG-IUS (Oderkerk et al., 2021). A RCT needs to be done to elucidate the real advantages and outcome of this combination (Oderkerk et al., 2022).

Conclusion

Considering pharmacological treatment of HMB without underlying pathology, the results of this review suggests the LNG-IUS seems to be the best option to reduce menstrual blood loss. However, it is advised to carefully listen what the woman wants, thinks, believes and in the end make a shared decision. Pharmacological treatment should be initiated by GPs as a surgical intervention can be avoided. However, GPs should also have knowledge about the surgical (minimal) invasive solutions, in order to make a balanced personal decision. Women who prefer non-hormonal treatment for some reason and who are not receptive to other first line drug treatment should also be given the opportunity to improve their quality of life by getting rid of disabling symptoms of heavy menstrual bleeding, by offering treatment with endometrial ablation or hysterectomy.

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