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Management of heavy menstrual bleeding

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Chapter 1

General Introduction

GENERAL INTRODUCTION

“And a woman was there who had been subject to bleeding for twelve years. She had suffered a great deal under the care of many doctors and had spent all she had, yet instead of getting better she grew worse. When she heard about Jesus, she came up behind him in the crowd and touched his cloak, because she thought, “If I just touch his clothes, I will be healed.” Immediately her bleeding stopped and she felt in her body that she was freed from her suffering”¹

Heavy menstrual bleeding (HMB) is a disorder of all ages and occurs in women in all cultures. In the first years of our era, the impact on a woman’s physical functioning was not the major burden, but she was also an outcast for the community. After all, she was unclean and no one was allowed to touch her nor did she touch others. Although a menstruating woman is generally no longer considered ‘unclean’ in most cultures, the women themselves often indicate that they feel dirty and are afraid about perceived odour due to the heavy bleeding.² Even today, HMB is still accompanied by social shame. Affected women generally perceive it as terrible to have visible blood stains on clothes or bedding and the major impact and fear of leaking causes women to develop comprehensive avoidance strategies. Many women no longer go anywhere where they cannot visit a toilet very quickly and they plan social activities outside their menstrual period.² HMB still has a major impact on psychosocial well-being and the subject remains a taboo to discuss with friends, family or a medical professional.

Definition and epidemiology

Twenty-five to fifty percent of menstruating women report experiencing HMB.³⁻⁵ However, the prevalence of HMB in general practice is much lower, because not every woman visits her doctor for this complaint.³ HMB has often be objectively defined as 80 ml or more of blood loss per menstrual period, measured with the alkaline haematin method. However, this measure is difficult to implement in clinical settings and in addition, the complaint of severe menstrual bleeding appears to correlate poorly with the objectively measured amount of bleeding.⁶ In current clinical guidelines, HMB is defined as cyclical heavy blood loss during menstruation which interferes with the daily activities of a woman.^{4,7,8} HMB not only impairs physical and psychosocial well-being, but also sexual function and

women with HMB regularly miss work.⁹ Furthermore, HMB can lead to iron deficiency anemia.^{10,11}

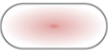
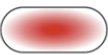




In less than half of the women an organic cause, such as fibroids, adenomyosis, a coagulation disorder, or a iatrogenic cause is found (copper intrauterine device or medication such as anticoagulants, misoprostol, corticosteroids and SSRIs). If no cause is found for HMB after additional examination, this is referred to as essential heavy menstrual blood loss. A physiological genetic variation in endometrial haemostasis may play a role.¹²⁻¹⁴ Furthermore, age is found to be an independent risk factor for essential HMB.¹⁵ In this thesis we focus on women with essential HMB.

Diagnosis

A structured medical history is the most important tool and first step in HMB diagnosis. In addition, vaginal examination can give an impression of the uterus size and the presence of large fibroids. Routine speculum examination is not indicated if there is cyclic blood loss without intermenstrual blood loss or contact bleeding. Furthermore, there are several tools that add to the accuracy of HMB diagnosis, including menstruation calendars, imaging techniques and laboratory tests.

Pictorial Blood Assessment Chart (PBAC)

A simpler method than the alkaline haematin method to assess the amount of blood loss is the Pictorial Blood Assessment Chart (PBAC), a menstruation calendar (see Figure 1). Both the Dutch General Practice and the Gynaecology guideline on HMB recommend to use the PBAC to gain a better understanding of the pattern and amount of menstrual blood loss.^{7,8} Furthermore, the PBAC is the most frequently used instrument in research settings to quantify the amount of menstrual bleeding.^{16,17} The woman herself estimates the degree of impregnation of each dressing or tampon when changing it and records it on a pre-printed card. With this card a total score can be calculated for the blood loss during one menstrual period. A total score of 150 or more makes the diagnosis of severe menstrual bleeding likely.¹⁸

PADS	DAY							
	1	2	3	4	5	6	7	8
 X 1	//	/	/	/	//	/		
 X 5		///	///	//				
 X 20		//	//					
TAMPONS	DAY							
	1	2	3	4	5	6	7	8
 X 1		/			/			
 X 5		//	///	//				
 X 10		/// /	///					
Points per day	2	137	101	21	3	1		

Total = 265 points

Figure 1. Pictorial Blood Assessment Chart (PBAC) – example

Transvaginal ultrasound

To exclude an underlying cause of HMB, such as fibroids, polyps or adenomyosis, a transvaginal ultrasound can be performed. In some regions in the Netherlands the ultrasound can be requested by the general practitioner, in other regions a woman must first be referred to the gynaecologist. If there is a suspicion of intracavitary abnormalities with transvaginal ultrasound, additional imaging with saline infusion sonography or hysteroscopy can be performed by the gynaecologist.

Laboratory tests

It is recommended to determine the haemoglobin level once during the evaluation of HMB, to investigate whether anaemia is present. Coagulation tests are indicated if HMB is present since menarche and if there are other symptoms suggesting a coagulation abnormality (excessive bleeding postpartum, after surgery or dental extraction, frequent bruising or epistaxis or a family history of bleeding symptoms).^{4,7,8} It is estimated that about 13% of women with HMB have an underlying bleeding disorder, most often von

Willebrand disease.¹⁹ However, the majority of studies on the prevalence of bleeding disorders among women with HMB are performed at gynaecology departments, not in primary care.

Treatment options in primary care

A woman can choose between non-hormonal therapy: tranexamic acid or nonsteroidal anti-inflammatory drugs (NSAIDs), and hormonal therapy: combined hormonal contraceptives, progestogens or the levonorgestrel intrauterine system (LNG-IUS), as a first-line treatment for HMB.

Oral medication

Tranexamic acid reduces the amount of menstrual blood loss due to an antifibrinolytic effect. NSAIDs reduce prostaglandin levels, which are elevated in women with HMB.²⁰ NSAIDs and/or tranexamic acid can be used during the first (heaviest) days of each menstruation. Advantages of non-hormonal therapy are maintaining one's own natural menstrual cycle and NSAIDs also reduce menstrual pain. Both can give gastrointestinal side effects and tranexamic acid is contra-indicated in women with a medical history or family members with a venous thromboembolism.

The oral contraceptive pill can be used daily with or without a stop week. Oral progestogens can be given in a short course of five to ten days, especially for acute HMB. Afterwards a withdrawal bleeding occurs, unless the combined oral contraceptive pill or prolonged progestogens are subsequently started. Common side effects of hormonal therapy are headache and spotting.

Treatment with the oral contraceptive pill shows a 43% reduction in blood loss in one study. Tranexamic acid gives a reduction of 29 to 58% and NSAIDs a reduction of 20-49%. There is insufficient evidence for a significant difference between combined oral contraceptives, NSAIDs or long course progestogens.²¹ Tranexamic acid seems to be more effective than NSAIDs and progestogen therapy.²²⁻²⁴ Data on the effectiveness of drug therapy for HMB are based on small, often underpowered studies. Because the available evidence does not show clinically important differences in effectiveness and acceptability among the pharmacological treatment options, treatment choice depends on the specific treatment characteristics and a woman's preference.

LNG-IUS

Since 2008, the LNG-IUS is recommended as one of the first-choice treatment options for HMB in the Dutch General Practice guideline *Vaginal bleeding*. The National Institute for Health and Care Excellence (NICE) in the United Kingdom even recommends the LNG-IUS as the first choice treatment over pharmacological treatment for HMB without identified pathology, fibroids less than 3 cm or suspected adenomyosis in their clinical guideline *Heavy menstrual bleeding*.⁴ Intrauterine devices were initially introduced as contraceptives. But the local release of levonorgestrel in the uterine cavity suppresses endometrial growth and therefore also reduces menstrual bleeding.²⁵ The general practitioner or the gynaecologist can insert the IUS without anaesthesia. Common side effects are spotting and progestogenic effects.

The LNG-IUS results in 71 to 96% blood loss reduction. However, the discontinuation rate is high: up to 50% within 5 years of follow-up and 46% of the women with HMB have undergone hysterectomy after 10 years of follow-up.^{26,27} Nonetheless, the discontinuation rate of the LNG-IUS is lower than that of oral medication, the LNG-IUS is more effective in reducing menstrual blood loss and patient satisfaction and quality of life are higher compared to treatment with oral medication.^{28,29}

Treatment options in secondary care

In secondary care, surgical treatments can be offered in addition to the drug treatment options that are also initiated in primary care. Until the eighties hysterectomy was the only alternative for women who were not helped with drug therapy. Although hysterectomy is 100% successful in treating HMB, it is associated with a risk of serious complications such as bleeding and infection. When performing a hysterectomy, both the uterus and the cervix can be removed (total hysterectomy) or the cervix can be retained (subtotal hysterectomy). There are three different routes of hysterectomy: by laparoscopy, laparotomy or vaginal.

A less invasive, uterus preserving, surgical treatment option is endometrial ablation. This local treatment aims to destroy or remove the endometrial tissue.³⁰ The procedure occurs in the operating room or in an outpatient setting by a gynaecologist under local or general anaesthesia. Endometrial ablation has a shorter hospital stay and recovery time compared to hysterectomy.³¹ First-generation endometrial ablation techniques

(endometrial laser ablation, transcervical resection of the endometrium, rollerball endometrial ablation) require visualisation of the uterus with a hysteroscope during the procedure. Second-generation techniques include endometrial cryotherapy, thermal balloon, microwave, hydrothermal, and bipolar radiofrequency endometrial ablation. Bipolar radiofrequency endometrial ablation (Novasure®) and thermal balloon endometrial ablation (Thermachoice®) are the most frequently used techniques in the Netherlands. Second-generation endometrial techniques seem to be superior to first-generation techniques because they require shorter operating times, can be performed more often with local anaesthesia and have comparable effectiveness compared with first-generation endometrial ablation. It is not known which second-generation technique is superior to others. In general, 83% of women have an acceptable blood loss reduction one year after treatment with second-generation ablation.³²

Thesis aim and rationale

Both the LNG-IUS and endometrial ablation have been proven effective in the treatment of HMB and are commonly used less invasive alternatives to hysterectomy. Though, the studies comparing the LNG-IUS with second-generation endometrial ablation have several limitations. Most studies are underpowered or have a relatively short follow-up. Satisfaction rates and quality of life seem to be similar after both treatments. Due to low quality and inconsistent evidence, it is not known if the LNG-IUS or second-generation endometrial ablation is more effective in reducing menstrual blood loss.²⁹ It is therefore unclear which treatment should be advised to women with HMB in whom pharmacological treatment was unsuccessful, unsuitable or undesired. Because the LNG-IUS is a less invasive, reversible treatment and less costly compared to endometrial ablation, our general aim was to investigate if starting treatment with the LNG-IUS is noninferior to starting with endometrial ablation in women with HMB. Moreover, we aimed to investigate if this treatment strategy is cost-effective.

Thesis outline

In **chapter 2** we used data of the Registration Network Groningen to investigate how many women consult their general practitioner with symptoms of HMB each year. We further describe the treatment started in the first months after diagnosis and

investigated if there were changes in prescribing practices after the revision of the Dutch General Practice guideline on vaginal bleeding in 2008, because the LNG-IUS is recommended as a first-choice treatment for HMB since then.

We performed a multicentre randomised controlled trial with a noninferiority design (the MIRA trial) to investigate if a strategy starting with the LNG-IUS is noninferior to a strategy starting with second-generation endometrial ablation (Novasure®) for treatment of HMB.

Chapter 3 describes the study design and in **chapter 4** we present the results after 24 months in terms of menstrual blood loss and menstrual bleeding pattern, reintervention rates, patient satisfaction, disease specific- and generic quality of life and sexual function.

In **Chapter 5** the results of a cost-effectiveness analysis from a societal perspective are presented, comparing the LNG-IUS strategy with the endometrial ablation strategy for the treatment of HMB over a 24 months' time horizon.

Many women recruited for the MIRA trial were not willing to participate because of a treatment preference. Therefore, we investigated in **chapter 6** in a consecutive sample of women with HMB what their preferences were regarding treatment with the LNG-IUS or endometrial ablation. We used a discrete choice experiment (DCE), filled in by the women before they were counselled for one or the other treatment option. With this DCE it is possible to estimate which characteristics have the most influence on a woman's choice.

In a minority of women, HMB is caused by a coagulation disorder. In **chapter 7** we looked at the presence of low coagulation Factor XI and Von Willebrand Factor levels and investigated if the treatment success of the LNG-IUS and endometrial ablation was different in these women compared to women with high coagulation factor levels.

The recruitment period of the MIRA trial suffered from a major delay, partly because general practitioners registered fewer patients than expected. In **chapter 8** we performed semi-structured interviews with general practitioners participating in the MIRA trial to identify barriers and facilitators for patient recruitment. With the results of this qualitative study we aimed to enhance patient recruitment for both the MIRA trial and future clinical trials in primary care.

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