Evaluation of treatment for heavy menstrual bleeding

Malou Herman

EVALUATION OF TREATMENT FOR HEAVY MENSTRUAL BLEEDING

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CHAPTER 1

Introduction

Heavy menstrual bleeding (HMB) is a common reason for general practice consultations in the primary care setting and specialist referral. About 30-50% of all menstruating women report that their periods are (very) heavy, and of these women 25% report that their periods are a marked or severe problem. HMB has a significant impact on the medical, socio-economic and psychological well-being of women. Therefore, there is a need for effective (diagnostic) strategies and treatment modalities.

HMB is defined as menstruation at regular intervals but with excessive flow and duration. The aetiology is diverse. HMB can be caused by abnormal blood clotting, disruption of hormonal regulation or uterine pathology (e.g., fibroids, polyps, adenomyosis). The cause of the HMB should, of course, be investigated first.
Clinically, HMB is defined as blood loss of more than 80mL per cycle, a definition given by Hallberg et al. However, the 80-mL criterion of blood loss is of limited clinical usefulness. The diagnosis and treatment of patients appears to be unrelated to the volume of blood loss. Women's perception of the severity of bleeding does not always correlate with the objective amount of blood loss. Warner et al. found that merely 34% women exceed the 80mL threshold.[11] Thus, not only the amount of bleeding, but probably also the way these women cope with the problem plays an important role in their complaints. Therefore, one should ascertain whether there are additional (psychological) factors that could cause women to present with complaints of HMB. For example, women in vulnerable psychological states are more likely to have coping difficulties regarding their gynaecological status than women who are more psychologically healthy.[12,13] Thus, the 80-mL criterion should be challenged as well as the idea that volume captures the complaints of those suffering from heavy periods. Perhaps a more patient-centred definition should be used and the HMB criteria redefined. Nevertheless, defining the blood loss problem women experience should be the first step in diagnosing. Any complaints about blood loss should therefore be fully examined. Only after the underlying cause has been identified can the best treatment option be chosen.

Diagnosis of HMB

Objectively knowing whether or not the blood loss is excessive could be very beneficial for both patient and clinician. This determination will not only clarify the complaint, but it will also influence the choice and expectations of treatment. A few methods have been developed for measuring menstrual blood loss (MBL).

The gold standard for the measurement of MBL is alkaline hematin extraction. Women need to collect all of their menstruation blood including all used towels or tampons. This method is not practical for daily use and is only used in research. Another simplified method involves counting the number of used towels or tampons, but Fraser et al. did not find a correlation between the numbers and the volume of blood loss. Therefore, this method is not used anymore. Higham et al. developed a subjective method to determine whether or not women meet the diagnosis of HMB: the Pictorial Blood Assessment Chart (PBAC). The PBAC is a measurement tool used to reliably predict HMB. The self-assessed PBAC consists of diagrams representing towels and tampons soiled to various degrees. Women are instructed to count their number of used towels or tampons each day and then divide them by the level of soiling. The chart is scored using the scoring system devised by Higham et al. This measurement method has a specificity and sensitivity of 80-90% when compared to the gold standard. [14,15] Other studies have confirmed the accuracy of the PBAC compared to the alkaline haematin extraction method for the diagnosis of HMB. Higham found that a PBAC score of >100 correlated with 80mL blood loss. For the definition of HMB, Janssen et al. recommended a cut-off of 185 points, while Zakherah recommended a cut-off at 150 points. A PBAC score of >150 points is most often used as an inclusion criterion in HMB studies.

Therefore, the PBAC is said to be a useful measurement tool for accurately diagnosing HMB (when we use the 80mL criteria) and it is also a frequently chosen outcome parameter in HMB studies. However, little is known about the meaning of the PBAC score, before and after treatment, or about its relation with success rate after treatment. In order to evaluate treatments, predict their effectiveness and inform patients about these predictions, clinicians need to know more about this measurement tool.

Treatment

In view of its high prevalence, an optimal treatment for heavy menstrual bleeding is of utmost importance. After exclusion of intracavitary pathology, many treatments can be considered to reduce the amount of blood loss. Treatment options for HMB include medicinal therapies and surgical procedures, such as endometrial ablation and hysterectomy.

Hormonal treatment with the oral contraceptive pill, or non-hormonal treatment with tranexamic acid or non-steroidal anti-inflammatory drugs (NSAID) are recommended as treatments of first choice by the Dutch guidelines and Royal

College of Obstetrics and Gynaecology (RCOG).[17,18] If these treatments fail, both guidelines prefer the use of the levonorgestrel-releasing intrauterine system (LNG-IUS) as the next therapeutic option. Nevertheless, endometrial ablation could also be considered and is already frequently used in daily practice. Both LNG-IUS and endometrial ablation are local solutions used to obstruct endometrium proliferation. Which of these two options is the most effective and which of these two options is preferred by women is yet unknown. Both questions should be evaluated.

LNG-IUS versus endometrial ablation

Intrauterine devices were initially introduced as contraceptives; however, since the addition of progestagen, these devices have also been used as treatment for HMB. The LNG-IUS can be applied easily by the general practitioner and is effective in reducing the amount of blood loss. Literature on the effectiveness of the LNG-IUS in HMB shows that it reduces menstrual blood loss by about 80-95%. For women who presented to primary care providers, the LNG-IUS was even more effective than usual medical treatment at reducing the effect of bleeding on quality of life. However, the LNG-IUS has considerable discontinuation rates – up to 38% within 2 years – due to side effects, such as irregular bleeding (spotting), pain, and/or systemic progestogenic side-effects.

As an alternative, endometrial ablation is also very effective at decreasing blood loss, with amenorrhea rates of up to 50% and satisfaction rates of about 90%. Endometrial ablation is performed by the gynaecologist in day-care or outpatient clinics with or without general anaesthesia. It is more invasive than the LNG-IUS because the aim of the procedure is to destroy or remove the endometrial tissue and, consequently this treatment is irreversible. Women need to know that it does not provide contraception and that it shows higher dysmenorrhoea rates.

The first-generation endometrial ablation techniques were performed with direct hysteroscopy vision. These techniques involved a long learning curve and involved the risk of absorption of the distension fluid (Glycine or Sorbitol), resulting in fluid overload, which can result in fatal hyponatremic encephalopathy. The second-generation techniques were developed to overcome these disadvantages and are now the safest and easiest techniques to perform.[4] Frequently used second-generation techniques are bipolar radiofrequency energy (Novasure), high temperature fluids within a balloon (Thermachoice, Thermablate, Cavaterm) and free, high temperature fluid (Hydrothermablator). Many of these second-generation ablation techniques have been evaluated for their short-term effect,

but literature reporting on long-term follow-up is limited. As the aim of ablative therapies is to offer patients a desirable and long-term solution, an adequate follow-up of these therapeutic interventions is still needed.

As mentioned, no evidence-based advice regarding the preferred choice between LNG-IUS or endometrial ablation can be given due to lack of sufficiently powered studies directly comparing both options. In the literature, seven trials compare the LNG-IUS with either transcervical resection of the endometrium or balloon ablation. A significantly lower PBAC score was reported for all women and a significantly lower mean reduction in PBAC score was reported in the surgical group.
Most outcomes showed no difference in satisfaction rates, amenorrhea rates, duration of menstruation, further surgical treatment or quality of life (QoL).[30,33- 37] However, these studies are small. Further, most of the studies have a short period of follow-up and contain a lot of non-compliance, which hinders the interpretation of outcomes. Besides, it is not known whether women would accept LNG-IUS side-effects to benefit from a less invasive procedure, or if they would reject hormonal treatment despite the fact that the other option is a more invasive procedure. Nevertheless, many women are keen to avoid hysterectomy and opt for a less invasive treatment, even when they are informed of the fact that success is not always assured.[1,27,38,39] Therefore, more research on the effectiveness of these minimally invasive options, and patients' preferences for them, is needed. The results would contribute to further improvement of patient counselling and therefore would hopefully lead to an increase in patient satisfaction.
All the subjects mentioned in this chapter (diagnosing HMB, evaluating blood loss, effectiveness of different treatments, patient' s preference) lead to the following question: should HMB be studied using objective assessment with menstrual diaries or subjective assessment such as satisfaction or (disease specific) QoL? On what aspect of HMB should we focus? There is no standardised outcome to define the effect of treatment for HMB and a variety of primary outcomes are currently used. Therefore, it is of utmost importance for the interpretation of data that there is consistency in the choice and definitions in primary and secondary outcomes. Only then can clinicians give their patients well-founded advice.

This thesis deals with the (long-term) effectiveness of endometrial ablation and patient preference for second-generation ablation techniques versus LNG-IUS. Moreover, this thesis provides insight into the outcome measures used in previous HMB research and investigates the value of the PBAC score as an outcome.

Outline of the thesis

This thesis aims to answer the following questions:

1. What is the effectiveness of second-generation ablation techniques at long-term follow-up?
2. Is there a relation between the Pictorial Blood Assessment Chart score and treatment outcome?
3. Do patients prefer LNG-IUS or endometrial ablation in the treatment of heavy menstrual bleeding?
4. What is the effectiveness of LNG-IUS compared to endometrial ablation in the treatment of heavy menstrual bleeding?
5. What outcome measures are used in heavy menstrual bleeding studies?

To answer these questions we conducted several studies which are described below. The results of these studies are presented in this thesis.

Chapter 2 gives an overview of the diagnosis of HBM, paying special attention to women's perception of blood loss.

Chapter 3 presents 5-year follow-up results of a randomised controlled trial comparing the effectiveness of two second-generation ablation techniques: bipolar radiofrequency impedance controlled endometrial ablation (Novasure®) and hydrothermablation (HTA®).

Chapter 4 evaluates the results at 10-year follow-up after a randomised controlled trial comparing the effectiveness of two second-generation ablation techniques: bipolar radiofrequency impedance controlled endometrial ablation (Novasure®) and balloon endometrial ablation (Thermachoice®).

Chapter 5 focuses on the meaning of the PBAC score and the outcome after endometrial ablation. We included raw individual patient data (IPD) from all randomised controlled trials regarding endometrial ablation as a therapy for HMB.

Chapter 6 investigates patient preferences for endometrial ablation and LNG-IUS. A discrete choice experiment was used to assess women's preferences.

Chapter 7 proposes a multicenter randomised controlled trial in which two strategies are compared in the treatment of heavy menstrual bleeding: the LNG-IUS and endometrial ablation. This will be organised in a network infrastructure in which both general practitioners and gynaecologists collaborate. The study focuses on (cost-) effectiveness, patient satisfaction and quality of life.

Chapter 8 reviews the choice and consistency of primary outcomes used in randomised controlled trials and systematic reviews for the treatment of HMB.

Chapter 9 summarises the data presented in this thesis. A Dutch version is included.

Chapter 10 provides a general discussion with suggestions for further research.

Chapter 11 contains the valorisation addendum, which explains the significance of this research.

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CHAPTER 7

Is the Pictorial Blood Assessment Chart (PBAC) associated with treatment outcome after endometrial ablation for heavy menstrual bleeding?

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IPD Meta-analysis Collaborative Group

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Abstract

Objective: The Pictorial Blood Assessment Chart (PBAC) is a validated tool that is used to diagnose heavy menstrual bleeding (HMB). Knowledge of the impact of its score and its effect on outcome could have implications for using the PBAC as an outcome measurement in future HMB studies and as a tool to evaluate the treatment effect in research and clinical practice. Our aim was to relate PBAC scores to other measures of success of a treatment for heavy menstrual bleeding.

Design: Individual patient data (IPD) of randomised controlled trials studying women with heavy menstrual bleeding.

Method: We included studies if they had studied second generation endometrial ablation techniques and had collected PBAC scores for both baseline and follow-up. The effectiveness of treatment was scored as satisfaction or re-intervention (yes/no) 12 months after treatment. We related these outcomes to the PBAC score at 12 months after treatment and to PBAC decrease between baseline and 12 months of follow-up.

Results: We studied data of 900 patients included in 9 studies. The median PBAC score at 12 months was 7 (0-2500). The overall satisfaction rate was 89% and the overall re-intervention rate was 7.2%. A clear association was found between the PBAC at 12 months follow-up and satisfaction (odds ratio(OR) 0.16, 95% confidence interval (CI) [0.11-0.24]) and surgical re-intervention (OR 2.3, 95% CI [1.8-2.8]). PBAC decrease was also associated with satisfaction (OR 2.0, 95%CI [1.7-2.3]) and surgical re-intervention (OR 0.69, 95%CI [0.63-0.75]). PBAC-scores at 12 months that corresponded best with satisfaction occurred at 59 points (sensitivity 77%, specificity 88%) or a decrease of around 90% in PBAC score. The best PBAC score for re-intervention occurred at 98 points (sensitivity 84%, specificity 84%) or a decrease of 75% in score.

Conclusion: PBAC scores 12 months after treatment are significantly associated with satisfaction and re-intervention rates. We propose to use the PBAC in research as primary endpoint in studies on HMB and in clinical practice as a measure to assess the effectiveness of treatment.

Introduction

Heavy menstrual bleeding (HMB) is one of the main reasons to consult a general practitioner or gynaecologist and many treatments options, such as endometrial ablation, are available. HMB is defined as menstruation at regular intervals but with excessive flow and duration. Clinically, HMB is defined as blood loss of more than 80mL per cycle and to diagnose HMB the Pictorial Blood Assessment Chart (PBAC) is used[1,2]. However, it is unclear if we can also use the PBAC score as an evaluation tool for the treatment effect.

The Pictorial Blood Assessment Chart (PBAC) is a semi-quantitative measurement tool. Women are instructed to count their number of used towels or tampons each day and then divide them by level of soiling. The chart is scored using the scoring system devised by Higham et al. This measurement method has a specificity and sensitivity of 80-90% when compared to the gold standard, alkalin hematin method. Most studies use a score >150 points to define HMB. A PBAC score of 150 correlates with >80mL blood loss. Although 150 points is often used as a frequently chosen cutoff point to diagnose HMB, it is uncertain whether women after treatment are satisfied with a score closely below 150 points. Some women might expect amenorrhea while others could be satisfied with, for example, 50% decrease in score. In the literature, many studies use the height or decrease in PBAC as an outcome parameter. It is, however, unknown what the valuation is of these scores by women suffering HMB.

So, although the PBAC is considered a validated tool to diagnose HMB at a cut-off of 80mL blood loss per cycle, it is unknown if it is a useful tool to assess the effectiveness of HMB treatment, both in a research setting as well as in a clinical setting. Therefore, knowledge on the height of these scores in relation to the valuation of outcome of treatment is of great importance.

Method

Data collection

We used raw individual patient data (IPD) of studies that were collected for an analysis coordinated by the Birmingham Clinical Trials Unit. In 2012, Daniels et al. performed a network meta-analysis comparing the effectiveness of endometrial ablation methods. For this purpose, the study group created a database consisting

of IPD of randomised controlled trials (RCT) regarding second generation endometrial ablation for HMB. We refer to that paper for a full report of selection procedure and data processing of participating RCT's.[8] In short, they included 19 trials published between inception and 2011. We updated this database by looking for the newest endometrial ablation studies published between May 2010 and November 2013. Three new trials were added to this database.

We first selected the studies that evaluated second-generation ablation in at least one randomization arm. We only included data from patients that had undergone a second generation endometrial ablation who had PBAC scores collected at baseline and follow-up. Data until 12 months of follow-up (the most popular follow-up time point) were used for analysis, or results at 6 month if data were not available at 12 months.

Outcome measures were defined as satisfaction (yes/no) and surgical re-intervention (yes/no). Satisfaction and reintervention rates were collected at 12 months off follow-up. Re-intervention could be a hysterectomy or a re-ablation. Women who had a surgical re-intervention were defined as dissatisfied after their initial ablation treatment. The authors used different satisfaction scales in their papers, so the trial unit recoded these results to a simplified scale; satisfied or dissatisfied.

Statistical analysis

We compared the PBAC scores and measures of effectiveness. Effectiveness was measured as satisfaction with the treatment effect (yes/no) or surgical re-intervention (yes/no). We provided box-and-whisker plots to express PBAC scores against both satisfaction (yes/no) or re-intervention (yes/no).

A logistic regression analysis, with correction for study, was performed to predict the probability for satisfaction and re-intervention after 12 months of follow-up, using absolute PBAC scores at 12 months of follow-up (PBAC12m) and percentage change, i.e. 100% * (PBACb - PBAC12m)/PBACb.

We then calculated the 75th percentile of the PBAC score of each study and repeated the analysis for the absolute PBAC scores using multiples of the 75th percentile. We performed this analysis to normalise data from the different studies so that individual test results could be compared. We used the P75, as patients can also score a zero on the PBAC scale, which means amenorrhea, and some studies could have a median of zero.

Table 1: Baseline characteristics of the included studies. Data are in numbers (n), years , mean (±standard deviation) or median (min-max).

Study	Technique	Frequency (n)	Age (years)	PBAC Baseline	PBAC 12 months mean	PBAC 12 months median	PBAC 12 months 75th percentile	Satisfied women (%)	Re-intervention after initial treatment (%)
Abbott '02	NovaSure	37	41	453	88	8 (0-1720)	62	87%	9%
	Cavaterm balloon	18							
Bongers '04	Thermachoice	43	43	731	86	10 (0-1480)	68	86%	7%
	NovaSure	83							
Brun '06	Cavatherm balloon	30	46	503	46	19 (0-410)	54	95%	0%
Busfield '05	Thermablate	41	41	502	110	79 (3-465)	149	-	19%
Cooper '04	Microwave	209	40	453	10	0 (0-248)	4	98%	1%
Hawe '03	Laser	1	42	353	29	4 (0-251)	34	81%	16%
	Cavaterm balloon	37							
Meyer '98	Thermachoice	137	40	553	53	21 (0-457)	61	94%	2%
Penninx '10	NovaSure	82	45	797	173	21 (0-2500)	100	78%	16%
	Hydrothermal Ablation	78							
Penninx '13*	NovaSure	52	45	944	98	14 (0-1450)	94	82%	9%
	Thermablate	52							
Total		**900**	**42 (±5.3)**	**630 (±567)**	**77 (± 211)**	**7 (0-2500)**		**89%**	**7%**

PBAC = Pictorial Blood Assessment Chart
* Unpublished data

We also used receiver operating characteristic (ROC) curve analysis to assess the diagnostic value of PBAC score for satisfaction or re-intervention. The area under the ROC curve (AUC) as well as the sensitivity and specificity at different PBAC scores were reported. The sensitivity and specificity of the best cut-off value (point closest to left corner of ROC curve) was also reported. As a sensitivity analysis, the ROC curve was also assessed using the aforementioned logistic regression models, in which we corrected for study by using the predictive probability. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 21.0, Armonk: NY, IBM Corp).

Results

Nine trials, reporting on the individual data of 900 women, met our inclusion criteria and were included in this study (Table 1 [9-17]). Eight different second generation techniques were evaluated in the included studies. Study sizes varied between 30 and 209 participants. Details and baseline characteristics of the included trials are summarised in Table 1. The overall satisfaction rate was 89% (78-98%). The overall reintervention rate was 7.2% (0-19%). Figure 1 and 2 show the box-and-whisker plots of absolute PBAC12m scores for both outcomes.

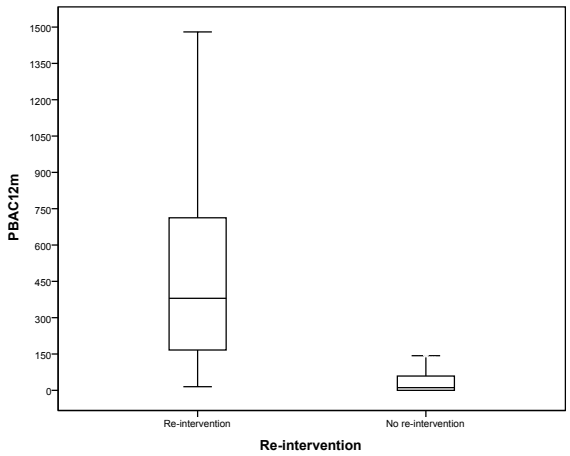

Figure 1: A box-and-whisker plot expressing the distribution of absolute PBAC score at 12 months in relation to satisfaction

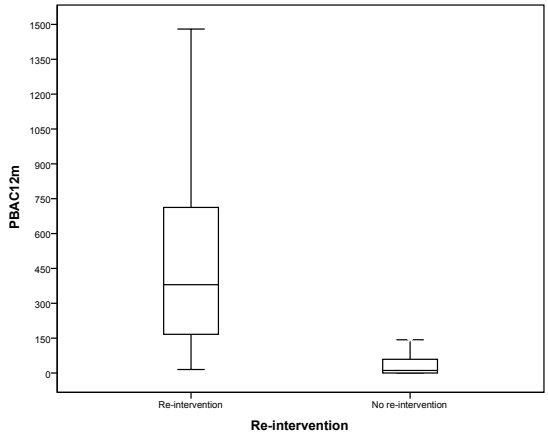

Figure 2: A box-and-whisker plot expressing the distribution of absolute PBAC scores at 12months in relation to re-intervention.

Logistic regression with adjustment for study gave unreliable results. The trial by Busfield et al. had a relatively small sample size and did not use satisfaction as an outcome measurement. Therefore, this study was excluded from the analyses for satisfaction. The trials by Brun et al. and Cooper et al. were the only two studies in which nearly none of the women received surgical re-intervention 12 months after treatment. These studies were therefore excluded from the analyses of surgical re-intervention.

PBAC score at 12 months

PBAC12m is strongly associated to satisfaction (OR 0.16 [95%CI 0.11-0.24]) and surgical re-intervention (OR 2.3 [95%CI 1.8-2.8]). Repeating the analysis for multiples of the P75 gave OR 0.8 [95% CI 0.74-0.86] for satisfaction and OR 1.6 [95% CI 1.4-1.8] for reintervention).

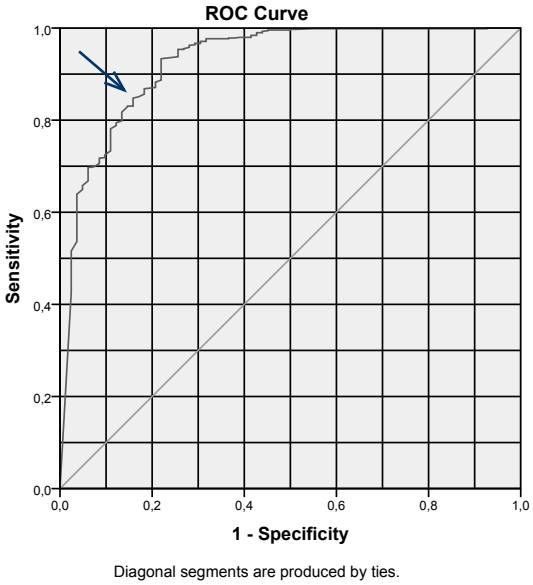

Figure 3: Receiver Operating Characteristic curve with regard to satisfaction at 12 months of follow-up for possible PBAC cutoff points

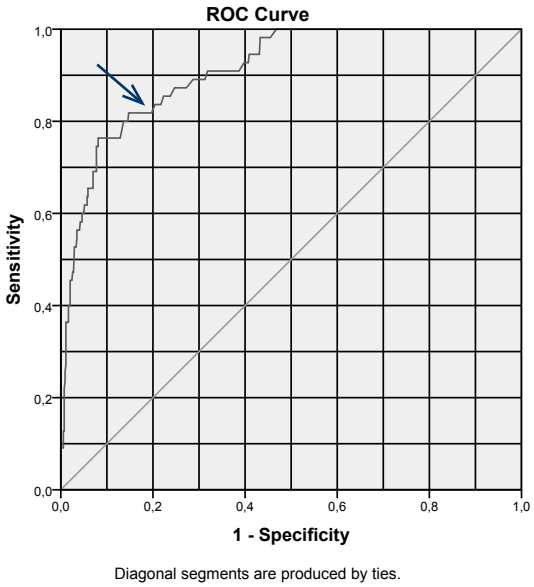

Figure 4: Receiver Operating Characteristic curve with regard to re-intervention at 12 months of follow-up for possible PBAC cutoff points

The ROC curve for satisfaction had an AUC of 0.93 (Figure 3). At PBAC12m the best cutoff score is 59 points, with a sensitivity and specificity of 0.85 and of 0.84, respectively. The sensitivity analysis shows similar results (AUC=0.93, sensitivity=0.84, specificity=0.83). For re-intervention, the ROC is comparable. The AUC is equal to 0.91 (Figure 4). The best cut-off value for PBAC12m is 98 points, with sensitivity of 0.82 and specificity of 0.85. After correction for study, the best cut-off value increases to 128 points, AUC to 0.94, sensitivity to 0.89 and specificity to 0.86. The sensitivity and specificity of different PBAC12m scores are given in table 2.

Table 2: Sensitivity and specificity for some specific PBAC12m scores regarding satisfaction and re-intervention

PBAC score	**Sensitivity %** satisfaction	**Specificity %** satisfaction	**Sensitivity %** re-intervention	**Specificity %** re-intervention
0	0.00	100	100	32
20	70	93	95	57
40	78	89	91	66
50	82	87	89	71
59*	**85**	**84**	**-**	**-**
60	85	83	87	75
80	90	78	84	80
98**	-	.-	82	85
100	93	78	80	85
120	95	74	76	89
140	96	73	76	90
150	96	72	76	91
160	97	70	76	92
180	97	69	71	92
200	98	64	66	93
413	100	45	-	-
1150	-	-	9	100

PBAC = Pictorial Blood Assessment Chart
* Best cutoff point in ROC for satisfaction
** Best cutoff point in ROC for re-intervention.

Percentage of change in PBAC

The percentage change in PBAC score is also strongly associated to satisfaction (OR 2.0 [95%CI 1.7-2.3]) and surgical re-intervention (OR 0.69 [95%CI 0.63-0.75]). The ROC curve for satisfaction is shown in Figure 5, where the AUC is 0.92. The best

cut-off value for the percentage change can be found at 89% with a sensitivity of 0.84 and specificity of 0.84. The sensitivity analysis shows a comparable cut-off point of 80%, with an AUC of 0.90 and a sensitivity of 0.85 and specificity of 0.81. The ROC curve for re-intervention has an AUC of 0.91 (figure 6).

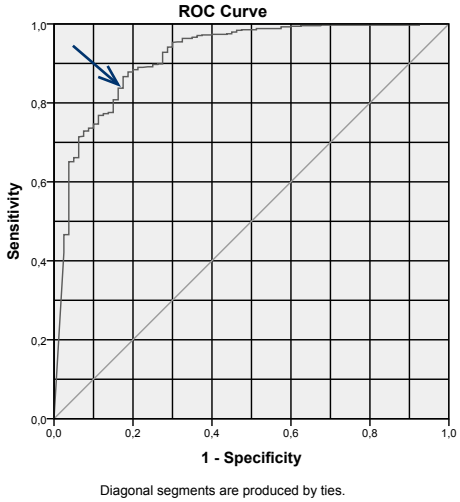

Figure 5: Receiver Operating Characteristic curve with regard to satisfaction at 12 months of follow-up for possible PBAC reduction (%) cutoff points

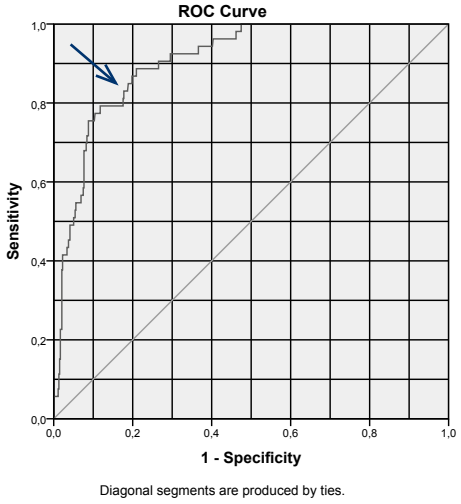

Figure 6: Receiver Operating Characteristic curve with regard to re-intervention at 12 months of follow-up for possible PBAC reduction (%) cutoff points

The cut-off point is 75% with a sensitivity of 0.79 and specificity of 0.88. After correction for study, the AUC is 0.93. The best cut-off value is then 74% with a sensitivity of 0.91 and a specificity of 0.86. Table 3 shows different percentages of reduction in PBAC with its sensitivity and specificity.

Table 3: Sensitivity and specificity for some percentages reduction in PBAC score regarding satisfaction and re-intervention

Reduction PBAC score (%)	**Sensitivity %** Satisfaction	**Specificity %** Satisfaction	**Sensitivity %** Re-intervention	**Specificity %** Re-intervention
0	100	21	23	98
10	100	27	28	98
20	100	32	38	98
30	99	40	43	96
40	99	49	49	95
50	98	46	55	94
60	97	61	59	93
70	96	66	74	91
75**			**77**	**88**
80	92	72	79	86
89*	**84**	**84**	-	-
90	82	84	90	72
100	42	100	100	31

PBAC = Pictorial Blood Assessment Chart
* Best cutoff point in ROC for satisfaction
** Best cutoff point in ROC for re-intervention

Discussion

Main findings

We studied the meaning of the Pictorial Blood Assessment Chart score (PBAC) after endometrial ablation. The PBAC score 12 months after treatment and reduction of PBAC score in percentages are significantly associated with satisfaction and re-intervention rates. PBAC demonstrated high accuracy for both treatment outcomes. The best cut-off value for PBAC at 12 months regarding satisfaction, with the highest sensitivity and specificity, can be found at 59 points or at a reduction of around 90% in PBAC score. For re-intervention this threshold lies at 98 points or a decrease of 75% in score. On the other hand, most women who

are unsatisfied have a reduction of less than 80% or a PBAC score higher than 80 points (sensitivity scores >90%).

Strength and limitations

The PBAC has not been evaluated as a tool to assess the effectiveness of a treatment before. By combining raw individual patient data of randomised controlled trials we were able to analyse a large patient population. A limitation is that we had to recode the outcome scales for every study to be able to combine them, as most studies reported different outcome measurement scales (e.g. satisfaction scales 3,4 or 5 points).

Interpretation

PBAC is a semi-quantitative measurement tool and is validated for the use of diagnosing heavy menstrual bleeding. A menstruation needs to exceed 150 points on the chart to diagnose HMB, but upto now it was unclear if the score was also associated with a treatment effect. [2] Only Pawar *et al.* investigated the impact of heavy menstrual bleeding, measured by the PBAC score, on the Qualtiy of life (QoL) and found a positive correlation: The higher the PBAC-score the lower the QoL. [7] However, they only studied baseline scores and did not evaluate scores after treatment. Other studies confirmed the accuracy of the PBAC compared to the alkaline hematin extraction method (gold standard) for the diagnosis of HMB. Higham found that a PBAC score of >100 correlated with 80mL blood loss, the definition for HMB. Janssen et al. recommended a cut-off of 185 points, while Zakherah recommended a cut-off at 150 points. A PBAC score of >150 points is most often used as an inclusion criterion in HMB studies.[2-4] Hald et al. explored the subjective perception of bleeding and the inter-individual and intra-individual variation of PBAC and found that women scored their period with normal blood loss if PBAC values were below 130 points. Nevertheless, all these above mentioned studies focused on the amount of blood loss for diagnosing HMB, not on the acceptability of the bleedings for women after treatment.[3-5] So these PBAC heights are not comparable to a group of women treated for HMB. How much blood loss after treatment is acceptable for women and how should we measure this? Although PBAC is a diagnostic tool, many studies have used the PBAC to evaluate blood loss after treatment. Remarkable, because it has never been studied for this purpose. So, actually it is not appropriate to base effectiveness conclusions on the PBAC measurement tool. Our study is the first study that investigated the

meaning of PBAC as an outcome tool. We found that a PBAC score of 59 points or a decrease of around 90% in score gives the highest sensitivity and specificity for satisfaction and no re-intervention for these treated women. This result is not comparable to the "normal period", indicated as <130point by Hald. These treated women seem to search for a lower amount of blood loss. We believe PBAC could now be a meaningful outcome measure and we should use the information of this study in future HMB studies. We propose to use the PBAC as primary endpoint in studies on HMB and to use it in clinical practice as a measure to assess the effectiveness of treatment. Of course, future studies must first validate the PBAC score after treatment.

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- J.Hawe, Countess of Chester Hospital ,Chester, UK;
- W.R. Meyer, data supplied by Ethicon, NJ, US
- J.P.M. Penninx, Maxima Medical Centre, Veldhoven, Netherlands

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CHAPTER 9

SUMMARY

Heavy menstrual bleeding (HMB) is a common reason for general practice consultations in the primary care setting and specialist referral. About 30-50% of all menstruating women report their periods as (very) heavy, and of these women 25% report that their periods are a marked or severe problem. HMB has a significant impact on the medical, socio-economic and psychological well-being of women. Therefore, there is a need for effective diagnostic strategies and treatment modalities. This thesis deals with the (long-term) effectiveness of endometrial ablation and patient preference for second-generation ablation techniques versus LNG-IUS. Moreover, this thesis also provides insight into the outcome measures used in previous HMB research and investigates the value of the PBAC score as an outcome.

Chapter 1 outlines the aim of this thesis which is formulated in five questions:

1. What is the effectiveness of second-generation ablation techniques at long-term follow-up?
2. Do patients prefer LNG-IUS or endometrial ablation in the treatment of heavy menstrual bleeding?
3. What is the effectiveness of LNG-IUS compared to endometrial ablation in the treatment of heavy menstrual bleeding?
4. Is there a relation between the Pictorial Blood Assessment Chart score and treatment outcome?
5. What outcome measures are used in heavy menstrual bleeding studies?

Prior to the discussion of the above questions, **Chapter 2** gives an overview of the diagnosis of HMB. The clinician must take into account the fact that there is a wide variation in menstrual cycles and amount of blood loss between women. This variation should be discussed with the patient as this information can sometimes be reassuring for her. Besides, objectively knowing whether or not the blood loss is excessive could be very beneficial for both patient and clinician. This determination will clarify the patient's complaint, and it will also influence the choice and expectations of treatment. The Pictorial Blood Assessment Chart (PBAC) score can help with diagnosis as it predicts HMB reliably. Nevertheless, besides the physical examination, we should also focus on women's perception of blood loss. Many women who seek treatment for HMB complain about their physical, social and emotional well-being. For each woman a thorough history should be taken to establish the true nature of her

symptoms. One should ascertain whether there are underlying factors that could cause these women to present with complaints of heavy menstrual bleeding. The amount of suffering that women experience from abnormal menstrual bleeding is not only dependent on the severity of the bleeding abnormality itself, but also on the way these women cope with it. Women in a vulnerable position are more likely to have coping difficulties than women in a stable position. Physical examination starts with standard gynaecological examination. In daily practice, imaging tests are widely used in the work-up for women with HMB. The diagnosis of HMB is mostly a combination of one of the following imaging tests: transvaginal ultrasonography (TVS); Saline/gel infusion sonography (SIS/GIS); hysteroscopy; and magnetic resonance imaging (MRI). The first step in imaging tests should be the transvaginal ultrasound. If this is inconclusive or if intracavity abnormalities are suspected, then the physician can perform a saline infusion sonography (SIS) or gel infusion sonography (GIS) to visualise the uterine cavity. Laboratory tests, endometrial sampling, hysteroscopy and MRI should only be performed when indicated.

What is the effectiveness of second-generation ablation techniques at long-term follow-up?

Chapter 3 and 4 focuses on this question.

Chapter 3 presents the 5 year follow-up results of a randomised controlled trial comparing the effectiveness of two second-generation ablation techniques: bipolar radiofrequency impedance controlled endometrial ablation (Novasure®) and hydrothermablation (HTA®). Patients were included between March 2005 and August 2007. One hundred and sixty women with heavy menstrual bleeding were randomly allocated to bipolar ablation or hydrothermablation. At 4–5 years follow-up, a questionnaire was sent to all the participants to register amenorrhea rates, re-interventions, and patient satisfaction. Response rates were 90% in the bipolar group and 83% in the hydrotherm group. Amenorrhea rates were 55.4% and 35.3% in the bipolar group and the hydrotherm group, respectively (relative risk [RR] 1.5, 95% confidence interval [CI] 1.05–2.3). The number of surgical re-interventions was 11 compared with 23 (RR 0.43, 95% CI 0.23–0.80). Overall, more women were satisfied in the bipolar group compared with the hydrotherm group. The results from this study showed that bipolar ablation is more effective than hydrotherm ablation 5 years after treatment.

Chapter 4 evaluates the results 10 years after a randomised controlled trial comparing the effectiveness of two second-generation ablation techniques: bipolar radiofrequency impedance controlled endometrial ablation (Novasure®) and balloon endometrial ablation (Thermachoice®). A follow-up questionnaire was sent to women 10 years after randomization. Main outcome measures were amenorrhoea rates, re-intervention and patient satisfaction. The response rate was 69/83 (83%) in the bipolar group and 35/43 (81%) in the balloon group. Amenorrhoea rates were 50/69 (73%) in the bipolar group and 23/35 (66%) in the balloon group (RR 1.1, 95% CI 0.83–1.5). Further treatment following initial ablation was reported in 21 cases, 14 in the bipolar group and nine in the balloon group (RR 0.9, 95% CI 0.63–1.3). Eight of these women required further treatment after 5 years, including two hysterectomies. Patient satisfaction in the bipolar group was 81% (56/69) compared with 77% (27/35) in the balloon group (RR 1.1, 95% CI 0.82–1.2).

This study concludes that ten years after treatment, the superiority of bipolar ablation over balloon ablation in the treatment of heavy menstrual bleeding is no longer evident. Although amenorrhea was the primary outcome in the initial study, for the long-term follow-up, the satisfaction rate and the hysterectomy rate are more useful for the evaluation of these ablation techniques. As we found that most re-interventions took place during the first 5 years after treatment, we conclude that evaluating outcome measures after short-term follow-up could help to predict long-term success in terms of the need for re-intervention.

Evaluating patient preference and effectiveness of LNG-IUS and endometrial ablation in the treatment of heavy menstrual bleeding

Usual care in the Netherlands implies two strategies for the treatment of heavy menstrual bleeding if drug therapy fails: the LNG-IUS and endometrial ablation. **Chapter 5** proposes a multicenter randomised controlled trial in which these two strategies are compared in the treatment of heavy menstrual bleeding. The LNG-IUS can be applied easily by the general practitioner (GP) and is effective at reducing the amount of blood loss; however, it has considerable discontinuation rates due to side effects, such as irregular bleeding (spotting). The contraceptive effect of the LNG-IUS is advantageous, but it has to be replaced every five years. On the other hand, removing the LNG-IUS is relatively simple and after that women regain their normal physiology. The alternative strategy is endometrial ablation, which is also very effective at decreasing menstrual bleeding and shows

high satisfaction rates. Nevertheless, this treatment is more invasive, it has to be performed by a gynaecologist, it is irreversible, it does not provide contraception and it has higher dysmenorrhea rates. Due to the lack of direct comparison of LNG-IUS with endometrial ablation, there is no evidence-based advice regarding the preference for one of these treatments. We propose a multicenter randomised controlled trial, organised in a network infrastructure in the Netherlands in which general practitioners and gynaecologists collaborate. Women ≥ 34 years of age with heavy menstrual bleeding, a Pictorial Blood Assessment Chart (PBAC) score exceeding 150 points and no desire for future children can participate in the trial. The primary outcome is the PBAC score at the 24-month follow-up. Secondary outcomes are patient satisfaction, complications, number of re-interventions, menstrual bleeding pattern, quality of life, sexual function, sick leave and costs. This study, which considers both the effectiveness and cost effectiveness of LNG-IUS versus endometrial ablation, may well improve care for women with heavy menstrual bleeding.

Besides effectiveness, women's preferences are also very important in clinical decision-making. Understanding considerations in decision-making can contribute to further improvement in treatment counseling and can eventually lead to higher patient satisfaction rates. **In Chapter 6** we perform a discrete choice experiment (DCE) to evaluate preferences between these two treatment options. We have selected the following characteristics: (1) procedure performed by gynaecologist or general practitioner (GP), (2) reversibility of procedure, (3) hormones, (4) dysmenorrhoea percentage, (5) use of contraception, (6) need to repeat the procedure after five years, (7) irregular bleeding percentage. Patient recruitment was performed in two Dutch hospitals and several general practices (GP) in the Netherlands. Women presenting with HMB were asked to participate. The main outcome measures were the relative importance of the characteristics and the willingness to make trade-offs between them.

One hundred and sixty-five women completed the questionnaire, 36 (22%) from GPs vs. 129 (78%) from gynaecologists. The most important characteristic was "Not requiring a treatment with hormones". Women had a preference for least side-effects, and an irreversible method that did not require a repeat procedure, no use of additional contraception, and a procedure performed by a gynaecologist above a GP. A treatment without hormones would be traded for a treatment with hormones in exchange for an absolute 15% (95% CI 6.1 to 23.8) decrease in dysmenorrhea. Thus, although the majority of the participants preferred

characteristics that are typical for endometrial ablation, women were prepared to trade off their preference.

Is there a relation between the Pictorial Blood Assessment Chart score and treatment outcome?

The Pictorial Blood Assessment Chart (PBAC) is a semi-quantitative measurement and is validated to diagnose HMB. Although 150 points is often used as a frequently chosen cut-off point to diagnose HMB, it was uncertain whether women would be satisfied with a score just below 150 points after treatment. **Chapter 7** focuses on the meaning of the PBAC score after treatment and its relation with the outcome after endometrial ablation. The Birmingham Clinical Trials Unit group created a database consisting of individual patient data (IPD) of randomised controlled trials (RCT) regarding second-generation endometrial ablation for HMB. We used the raw IPD of these studies. Nine trials met our inclusion criteria and were included in this study. In total these nine trials report on the individual data of 900 women. We compared the PBAC scores and measures of effectiveness. Effectiveness was measured as satisfaction with the treatment effect (yes/no) or surgical re-intervention (yes/no). The median PBAC score at 12 months was 7 points (range 0-2500). The overall satisfaction rate was 89% and the overall re-intervention rate was 7%. A clear association was found between the PBAC at 12 months follow-up and satisfaction (OR 0.16, 95% CI 0.11-0.24) and surgical re-intervention (OR 2.3, 95% CI 1.8-2.8). PBAC decrease was also associated with satisfaction (OR 2.0, 95% CI 1.7-2.3) and surgical re-intervention (OR 0.69, 95%CI 0.63-0.75). PBAC scores at 12 months that corresponded best with satisfaction occurred at 59 points, which means a decrease of around 90% in PBAC score. On the other hand, most women who are unsatisfied have a reduction of less than 80% or a PBAC score higher than 80 points (sensitivity scores >90%).The PBAC cut-off point for re-intervention occurred at 98 points or a decrease of less than 75% in score.

What outcome measures are used in heavy menstrual bleeding studies?

Chapter 8 analyses the chosen primary outcomes and measurement tools used in HMB research.

Heavy menstrual bleeding (HMB) is a common problem with a variety of treatment options and many studies have been performed evaluating treatment effects.

The variety of interventions in combination with a large number of different outcomes has resulted in a diversity of studies performed in the field of HMB. Consistency in the choice and definition of primary and secondary outcomes is important for the interpretation of data and for the synthesis of data in systematic reviews or individual patient data meta-analysis (IPDMA). To give insight into the primary endpoints and outcome measures chosen in RCTs and systematic reviews regarding the treatment of HMB we performed a systematic review in **Chapter 8.** We included full reports of RCTs or systematic reviews regarding the treatment of HMB. The studies had to report on the treatment of HMB and had to have a predefined primary outcome, underpinned by a sample size calculation. In the end, 66 RCTs and 26 reviews were included for analysis.
Twelve different primary outcomes were reported by 66 RCTs, of which the most frequently reported were blood-loss related (44/66). Amenorrhoea was the most common blood-loss related primary outcome (16/44). PBAC was the tool most frequently used to measure blood loss (27/44). Satisfaction was the second largest primary outcome (13/66), but there was no consistency in how this was measured. Fourteen (54%) reviews pre-specified a single primary outcome, while all other reviews used composite primary outcomes. Blood loss was the most frequently studied outcome among all reviews (12/26).
In conclusion, our findings show that there is large heterogeneity in the primary outcomes used in studies evaluating the treatment of HMB. Blood-loss related outcomes are most frequently used in HMB studies. Nevertheless, there is lack of consensus on how to define and measure these blood-loss outcomes. We also found huge variation regarding the measurement tools used. Our study increases awareness of HMB studies globally and draws attention specifically to the fact that consensus on primary outcomes is lacking in HMB research.

Chapter 10 provides a general discussion and implementation suggestions for further research.

Chapter 11 contains the valorisation addendum and explains why my research is important.

CHAPTER 9

SAMENVATTING

Hevig menstrueel bloedverlies (HMB) is een veel voorkomende klacht in de huisartspraktijk en één van de belangrijkste reden voor een verwijzing naar een gynaecoloog. Ongeveer 30-50% van alle menstruerende vrouwen ervaart hun menstruatie als (erg) hevig, en 25% van deze vrouwen vindt dit een serieus probleem. HMB heeft een belangrijke invloed op zowel het medisch, sociaal-economisch als het psychologische welzijn van vrouwen. Daarom is er een behoefte aan effectieve diagnostische strategieën en behandelingen.

Dit proefschrift gaat over de (lange termijn) effectiviteit van endometriumablatie en de voorkeur van de patiënte voor de tweede generatie ablatie technieken versus het hormoonhoudend spiraal. Bovendien geeft dit proefschrift ook inzicht in de uitkomstmaten die gebruikt zijn in eerder HMB onderzoek en onderzoekt zij de waarde van de menstruatiescore kaart (PBAC) als uitkomstmaat.

Hoofdstuk 1 schetst het doel van dit proefschrift. Dit is geformuleerd aan de hand van een vijftal vragen:

1. Wat is de effectiviteit van de tweede generatie ablatie technieken bij een lange termijn follow-up?
2. Geven vrouwen de voorkeur aan het hormoonhoudend spiraal of aan endometriumablatie als behandeling van HMB?
3. Wat is de effectiviteit van het hormoonhoudend spiraal in vergelijking met endometriumablatie als behandeling van HMB?
4. Bestaat er een relatie tussen de score op de menstruatiescorekaart en de uitkomst van de behandeling?
5. Welke uitkomstmaten worden gebruikt in HMB studies?

Voorafgaand aan de beantwoording van de bovenstaande vragen, geeft **Hoofdstuk 2** een overzicht van de diagnostiek bij HMB. Allereerst dient de arts rekening te houden met het feit dat er een grote variatie in menstruatiecyclus en bloedverlies bestaat tussen vrouwen. Deze variatie dient met de patiënt te worden besproken aangezien deze informatie soms geruststellend voor haar kan zijn. Daarnaast kan het objectief vaststellen of het bloedverlies buitensporig is, ook zeer gunstig zijn voor zowel patiënt als arts. Inzicht in deze klacht zal immers het probleem van de patiënt verduidelijken, en daarmee zal het ook van invloed zijn op de keuze en de verwachtingen van de behandeling. De menstruatiescorekaart kan helpen bij de diagnose, omdat het betrouwbaar HMB kan voorspellen. Toch moeten we, naast objectief onderzoek, ons ook focussen op de perceptie van het

bloedverlies bij deze vrouwen. Veel vrouwen die een behandeling zoeken voor HMB klagen namelijk over zowel hun fysieke, sociale als emotionele welzijn. Voor elke vrouw zou een grondige anamnese moeten worden afgenomen om de ware aard van haar symptomen vast te stellen. Men moet nagaan of er andere onderliggende factoren bestaan die ertoe kunnen leiden dat deze patiënten zich presenteren met klachten van HMB. De ernst van het lijden dat vrouwen met HMB ervaren, hangt namelijk niet al.leen af van de hoeveelheid bloedverlies, maar ook van de manier waarop deze vrouwen omgaan met hun klacht. Vrouwen in een kwetsbare positie hebben meer kans problemen te ervaren dan vrouwen in een stabiele positie.

Het lichamelijk onderzoek begint altijd met standaard gynaecologisch onderzoek. Daarnaast worden in de dagelijkse praktijk veel beeldvormende onderzoeken ingezet in de work-up voor vrouwen met HMB. Voor de diagnose wordt meestal een combinatie van een van de volgende beeldvormende onderzoeken gebruikt: transvaginale echoscopie; saline/gel infusie echografie (SIS/GIS); hysteroscopie; en magnetische resonantie imaging (MRI). De eerste stap in beeldvormend onderzoek is de transvaginale echografie. Als hierbij geen uitsluitsel verkregen wordt, of als intracavitaire afwijkingen worden vermoed, dan kan de arts saline infusie echografie (SIS) of gel infusie echografie (GIS) uitvoeren om het cavum uteri te visualiseren. Laboratorium onderzoek, endometrium bioptie, hysteroscopie en/of MRI zouden enkel op indicatie verricht moeten worden.

Wat is de effectiviteit van de tweede generatie ablatie technieken bij een lange termijn follow-up?

Hoofdstuk 3 en 4 richten zich op deze vraag.

Hoofdstuk 3 presenteert de 5 jaars follow-up resultaten van een gerandomiseerd onderzoek naar de effectiviteit van twee tweede generatie ablatie technieken: bipolaire ablatie van het endometrium (Novasure®) in vergelijking met hydrothermablatie (HTA®). Patiënten werden geincludeerd tussen maart 2005 en augustus 2007. Honderdzestig vrouwen met HMB werden gerandomiseerd tussen bipolaire ablatie of hydrothermablatie. Ongeveer 4-5 jaar na de behandeling, werd een vragenlijst gestuurd naar alle deelnemers om amenorroe, re-interventies, en tevredenheid van de vrouwen te registreren. 90% van vrouwen in de bipolaire groep en 83% van de vrouwen in de hydrotherm groep voltooiden de vragenlijst. Het percentage amenorroe was 55% in de bipolair groep en 35% in hydrotherm

groep, (RR 1.5, 95% CI 1.05-2.3). Het aantal chirurgische re-interventies was 11 versus 23 (RR 0.43, 95% BI 0.23-0.80). In de bipolaire groep waren significant meer vrouwen tevreden met het resultaat van de behandeling dan in de hydrotherm groep. De resultaten van deze studie laten zien dat bipolaire ablatie effectiever is dan hydrothermablatie 5 jaar na behandeling.

Hoofdstuk 4 evalueert de resultaten 10 jaar na een gerandomiseerd onderzoek, waarin ook twee tweede generatie ablatie technieken werden vergeleken: bipolaire endometriumablatie (Novasure®) en ballonablatie (THERMACHOICE®). Een follow-up vragenlijst werd verstuurd naar de deelnemende vrouwen 10 jaar na randomisatie. De belangrijkste uitkomstmaten waren: amenorroe, re-interventies en tevredenheid van de vrouwen. 69/83 (83%) vrouwen in de bipolaire groep en 35/43 (81%) in de ballon groep vulden de vragenlijst in. Amenorroe aantallen waren 50/69 (73%) in de bipolaire groep en 23/35 (66%) in de ballon groep (RR 1.1, 95% CI 0.83-1.5). Verdere behandeling na initiële ablatie werd gemeld in 21 gevallen, 14 in de bipolaire groep en negen in de ballon groep (RR 0.9, 95% CI 0.63-1.3). Acht van deze vrouwen kregen een re-interventie na 5 jaar, waaronder twee uterusextirpaties. Tevredenheid van de patiënt in de bipolaire groep was 81% (56/69) in vergelijking met 77% (27/35) in de ballon groep (RR 1.1, 95% CI 0.82-1.2). Deze studie concludeert dat tien jaar na de behandeling, de superioriteit van bipolaire ablatie ten opzichte van ballon ablatie in de behandeling van HMB niet meer evident aanwezig is. Hoewel amenorroe de primaire uitkomstmaat in de initiële studie was, lijken voor de lange termijn follow-up de tevredenheid en de hysterectomie aantallen beter bruikbaar te zijn voor de evaluatie van deze technieken. Aangezien deze studie laat zien dat de meeste re-interventies plaatsvonden tijdens de eerste 5 jaar na de behandeling, kunnen we concluderen dat evaluatie van de uitkomstmaten na korte-termijn follow up zouden kunnen helpen om lange termijn success, in termen van de behoefte aan re-interventies, te voorspellen.

Evaluatie van patiënten preferentie en effectiviteit van het hormoonhoudend spiraal versus endometriumablatie als behandeling van HMB.

De gebruikelijke zorg in Nederland impliceert twee strategieën voor de behandeling van HMB als geneesmiddeltherapie niet voldoende is: het hormoonhoudend spiraal (Mirena®) en endometriumablatie. **Hoofdstuk 5** stelt een multicentrum

gerandomiseerde trial voor waarin deze twee strategieën worden vergeleken voor de behandeling van HMB. Het hormoonhoudend spiraal kan eenvoudig worden voorgeschreven en worden geplaatst door de huisarts en is effectief gebleken in het verminderen van de hoeveelheid bloedverlies. Echter, veel vrouwen discontinueren deze therapie wegens bijwerkingen, zoals onregelmatig bloedverlies (spotting). De anticonceptieve werking van het hormoonhoudend spiraal is een voordeel, maar het moet dan wel elke 5 jaar worden vervangen. Aan de andere kant, het verwijderen van het hormoonhoudend spiraal is relatief eenvoudig en vrouwen krijgen daarna weer hun normale fysiologie terug. De alternatieve strategie is endometriumablatie, wat ook zeer effectief is gebleken in het verminderen van menstrueel bloedverlies, bovendien zijn de tevredenheidpercentages hoog. Niettemin, deze behandeling is wel meer invasief, het moet worden uitgevoerd door een gynaecoloog, is onomkeerbaar, en heeft geen anticonceptieve werking. Bovendien laat het verhoogde dysmenorroe aantallen zien. Vanwege het ontbreken van een goede directe vergelijking van het hormoonhoudend spiraal met endometriumablatie, is er geen evidence based advies van voorkeur voor een van deze behandelingen. Wij stellen een multicentrum gerandomiseerde trial voor, welke georganiseerd wordt in een netwerk infrastructuur in Nederland waarin huisartsen en gynaecologen samenwerken. Vrouwen ≥ 34 jaar met HMB, een menstruatiescore van meer dan 150 punten en geen zwangerschapswens kunnen deelnemen aan deze trial. De primaire uitkomstmaat is de menstruatiescore 24 maanden na de behandeling. Secundaire uitkomsten zijn: tevredenheid van de patiënt, complicaties, het aantal re-interventies, het bloedingspatroon, kwaliteit van leven, seksuele functie, ziekteverzuim en kosten. Deze studie, die zowel de effectiviteit als kosteneffectiviteit van het hormoonhoudend spiraal versus endometriumablatie onderzoekt, kan de zorg verbeteren voor vrouwen met HMB. Naast effectiviteit, is de voorkeur van vrouwen ook erg belangrijk in klinische besluitvorming. Inzicht in overwegingen in de besluitvorming van vrouwen kan bijdragen aan een verbetering van behandelingen als ook in de begeleiding en kan hierdoor uiteindelijk ook leiden tot een hogere tevredenheid van de patiënt. In **Hoofdstuk 6** voeren we een discrete choice experiment (DCE) uit, waarbij we de voorkeur tussen de twee bovenstaande behandelingen evalueren. Hiervoor hebben we de volgende kenmerken geselecteerd: (1) de procedure wordt uitgevoerd door de gynaecoloog of huisarts; (2) de omkeerbaarheid van de procedure; (3) de behandeling bevat hormonen; (4) het dysmenorroe percentage (1% versus 10%); (5) het gebruik van aanvullende anticonceptie; (6) het herhalen

van de procedure na vijf jaar; en (7) het onregelmatig bloeden (spotting) percentage (0% versus 15%). De rekrutering van patiënten werd uitgevoerd in twee Nederlandse ziekenhuizen en een aantal huisartspraktijken in Nederland. Vrouwen die zich presenteerden met HMB werden gevraagd om deel te nemen aan de studie. De belangrijkste uitkomstmaten waren het relatieve belang van de kenmerken en de bereidheid om afwegingen te maken tussen deze kenmerken.
Honderdvijfenzestig vrouwen vulden de vragenlijst in, 36 (22%) vrouwen vanuit de huisartsen versus 129 (78%) vrouwen vanuit de gynaecologische praktijk. De belangrijkste eigenschap was "een behandeling zonder hormonen". Vrouwen toonden een voorkeur voor de minste bijwerkingen en een onomkeerbare methode die geen herhaling van procedure en geen gebruik van aanvullende anticonceptie behoeft. Bovendien werd een procedure uitgevoerd door een gynaecoloog geprefereerd boven een behandeling door de huisarts. Een behandeling zonder hormonen kon worden geruild voor een behandeling met hormonen in ruil voor een absolute 15% (95% CI 6,1-23,8) daling in dysmenorroe. Kortom, hoewel de meerderheid van de deelnemers de voorkeur gaf aan kenmerken die typerend zijn voor endometriumablatie, zijn vrouwen wel bereid om een trade-off te maken.

Bestaat er een relatie tussen de hoogte van de menstruatiescore (PBAC) en de resultaten van de behandeling?

De menstruatiescore, gemeten middels de Pictorial Blood Assessment Chart (PBAC), is een semi-kwantitatieve meting en is gevalideerd om HMB te diagnosticeren. Hoewel 150 punten vaak wordt gebruikt als afkapwaarde, is het onzeker of vrouwen ook tevreden zijn met een score net onder de 150 punten na de behandeling van hun bloedverlies. **Hoofdstuk 7** focust zich op de betekenis van de menstruatiescore na de behandeling en de relatie met de uitkomst na endometriumablatie.
De Birmingham Clinical Trials Unit creëerde een database met de gegevens van individuele patiënten (IPD) van gerandomiseerde studies (RCT) met betrekking tot de behandeling van HMB middels tweede generatie ablatie technieken. We gebruikten de ruwe data van deze studies. Negen studies voldeden aan onze inclusie criteria en werden opgenomen in de studie. In totaal rapporteerde negen studies over de benodigde gegevens, waarbij we in totaal de individuele gegevens van 900 vrouwen hadden. We vergeleken de menstruatiescores met de effectiviteituitkomsten. Effectiviteit werd gemeten als tevredenheid met het effect van de behandeling (ja/nee) of chirurgische re-interventie (ja/nee). De

gemiddelde menstruatiescore na 12 maanden was 77 punten. De algemene tevredenheid bedroeg 89% en het totale re-interventie percentage bedroeg 7,2%. Een duidelijk verband werd gevonden tussen de menstruatiescore na 12 maanden en tevredenheid (OR 0.16, 95% BI 0.11-0.24) en chirurgische re-interventie (OR 2.3, 95% CI 1,8-2,8). De procentuele daling in menstruatiescore was ook geassocieerd met tevredenheid (OR 2.0, 95% CI 1.7-2.3) en chirurgische re-interventie (OR 0.69, 95% BI 0.63-0.75). De menstruatiescore die het best overeenkomt met tevredenheid betrof 59 punten, of een daling van 80-90% in score. Anderzijds waren de meeste vrouwen ontevreden wanneer ze een daling van minder dan 80% of een menstruatiescore hoger dan 80 punten (sensitiviteit scores> 90%) hadden. De afkapwaarde voor re-interventie lag bij > 75 punten of een daling van minder dan 75% in score.

Welke uitkomstmaten worden gebruikt in HMB studies?

Hoofdstuk 8 analyseert de primaire uitkomstmaten en meetinstrumenten die gebruikt zijn in HMB onderzoek.

HMB is een veel voorkomend probleem met een verscheidenheid aan behandelingsmogelijkheden en waarbij er veel studies gedaan zijn naar het effect van deze verschillende behandelingen. Deze verschillende interventies in combinatie met een groot aantal verschillende uitkomstmaten heeft geleid tot een te grote diversiteit van studies op het gebied van HMB. Samenhang in de keuze en de definitie van primaire en secundaire uitkomstmaten is van belang voor de interpretatie van de gegevens en voor de synthese van gegevens in systematische reviews of individuele patiënten data meta-analyses (IPDMA). Om inzicht te geven in de gekozen primaire eindpunten en uitkomstmaten in RCT's en systematische reviews met betrekking tot de behandeling van HMB hebben we een systematische review uitgevoerd, welke beschreven staat in **Hoofdstuk 8**. We hebben alle RCT's en systematische reviews over de behandeling van HMB geincludeerd. De studies dienden over de behandeling van HMB te gaan en moesten een vooraf gedefinieerde primaire uitkomstmaat rapporteren, ondersteund door een berekening van de steekproefgrootte. Uiteindelijk konden 66 RCT's en 26 systematische reviews worden geincludeerd voor de analyses.

Twaalf verschillende primaire uitkomsten werden gevonden in 66 RCT's, waarvan de meest frequent gekozen groep van uitkomsten bloedverlies gerelateerd was (44/66). Amenorroe was de meest voorkomende bloedverlies gerelateerd primaire uitkomstmaat (16/44). PBAC was het meest gebruikte meetinstrument

(27/44) om bloedverlies te meten. Tevredenheid was de tweede grootste primaire uitkomstmaat (13/66), maar er werd geen consistentie gevonden in de manier waarop deze werd gescored. Veertien (54%) reviews onderzochten één primaire uitkomstmaat, terwijl alle andere reviews samengestelde primaire uitkomsten hadden gedefinieerd. Bloedverlies was de meest bestudeerde uitkomst in alle reviews (12/26).
Concluderend blijkt uit onze bevindingen dat er een grote heterogeniteit voorkomt in de gebruikte primaire uitkomsten in studies die de behandeling van HMB onderzoeken. Bloedverlies gerelateerde uitkomsten worden het meest gebruikt in HMB studies. Toch is er een gebrek aan consensus over de definiëring en meting van deze bloedverlies uitkomsten. We vonden ook een enorme variatie ten aanzien van de gebruikte meetinstrumenten. Onze studie vergroot de bewustwording over wat we wereldwijd aan het onderzoeken zijn ten aanzien van HMB behandelingen en vestigt de aandacht specifiek op het feit dat er géén consensus over de primaire uitkomsten bestaat.

Hoofdstuk 10 geeft een algemene discussie en implementatie voor verder onderzoek weer.
Hoofdstuk 11 bevat het valorisatie addendum en legt uit wat het belang is van mijn onderzoek.

CHAPTER 10

General Discussion

General discussion

The treatment of heavy menstrual bleeding (HMB) has been studied for many years as several different techniques and medical treatments have been developed. HMB has attracted so much medical attention because it is a major health problem and has a significant impact on the medical, social economic and psychological well-being of women. Clinicians are looking for a treatment that suits the complaints and preferences of the women affected by this condition.The studies presented in this thesis focus on the effectiveness of different treatments. We also explore patient preference and question the outcome measures currently used for HMB studies. Nevertheless, there are still some gaps in HMB research which we outline below.

LNG-IUS or endometrial ablation

In view of its high prevalence, finding the optimal treatment for heavy menstrual bleeding is of utmost importance. As we discuss in this thesis, usual care in the Netherlands implies two strategies for the treatment of heavy menstrual bleeding if drug therapy fails. The first is the LNG-IUS, which can be applied easily by the general practitioner (GP) and is effective at reducing the amount of blood loss; however, it has considerable discontinuation rates due to side effects, such as irregular bleeding (spotting). [1,2] The contraceptive effect of the LNG-IUS is advantageous, but it has to be replaced every 5 years. On the other hand, removing the LNG-IUS is relatively simple and after that women regain their normal physiology. The alternative strategy is endometrial ablation, which is also very effective at decreasing menstrual bleeding and shows high satisfaction rates. [3-6] Nevertheless, this treatment is more invasive, it has to be performed by a gynaecologist, it is irreversible, it does not provide contraception and it has higher dysmenorrhea rates. [7] Large randomised controlled trials comparing LNG-IUS with endometrial ablation are lacking and hence no advice can be given regarding which of these treatment possibilities is better. When we estimate that treatment for heavy menstrual bleeding involves many women annually, the potential savings that would result from implementing the best strategy are investigated in the study proposed in chapter 5. This is the first study that compares LNG-IUS and endometrial ablation and it will be organised in a network infrastructure in which both GPs and gynaecologists collaborate. Its study population is larger than those of other, similar trials and it has a long-term follow-up of 2 years. Besides the

objective outcome PBAC, we also measure patient satisfaction, quality of life (QoL) and sexual function. Due to this study's design and outcome measures, the results will be applicable for a large group of women suffering from heavy menstrual bleeding.

Is 80mL blood loss indeed heavy menstrual bleeding?

Clinically HMB is defined as blood loss of more than 80mL per cycle, a definition given by Hallberg et al.[8] Hallberg divided women in mL groups, whereby the most extreme endpoint of this range (80 mL) was adopted as the clinical threshold for HMB. Unfortunately, this upper level was not further subdivided. Women in this group had a significantly higher risk of having anaemia than women with losses in the lower mL categories. Therefore he considered menstrual bleeding >80 mL as more pathological. Janssen et al. questioned this cut-off point and reported in their study that not 80mL, but menstrual bleeding above 120 mL gave the highest percentage of women with anemia. Nevertheless, the limitations of both studies are that the cut-off volume is based on the occurrence of anaemia. Yet, a haemoglobin threshold should not be used for diagnosis of HMB. As written in chapter 2, the absence of anaemia does not exclude the diagnosis of HMB, as 20% of women with HMB have normal haemoglobin.[9] Another important research gap in these studies is women's perception of menstrual bleeding. As pointed out before, there is discordance between women's subjective experience of menstruation and actual amounts of menstrual blood loss. High variations are shown inside groups and there are large overlaps between the groups of woman who assessed their blood loss as minimal, normal and heavy.[10] Only 40-50% of women with complaints of HMB experience blood loss exceeding 80 mL.[11,12] Why is this? Perhaps the reason for this is that not only the amount of bleeding, but also the way these women cope with their menstruation plays an important role. For example, women in a vulnerable psychological position are more likely to have coping difficulties regarding their physical status than women in a stable psychological position.[13,14] Therefore, one should also ascertain whether there are additional (psychological) factors that could cause women to present with complaints of HMB. There is also evidence that lack of understanding between women with HMB and their doctors is present.[15] A community survey by Santer et al. reports that the main problem for many women was the change of their cycle. A range of menstrual symptoms, not only heavy bleeding, and their impact on everyday life bothered these women. Santer et al. recommend first clarifying the

presenting problem and providing help and advice for this, as well as excluding serious disease. Sometimes simple approaches, such as help with analgesia, may be all that is required.[15,16] If women receive inappropriate care or get unexpected results, this will also influence the actual and perceived efficacy of treatment modalities. Therefore, not only should the 80-mL criterion be challenged, but also the idea that volume captures the complaints of heavy periods. Defining the problem women experience should be the first step. Any complaints about blood loss should therefore be fully examined. Only after identifying the underlying cause can the best treatment option be chosen.

Future studies should focus on the following aspects. First, it must be determined what entails a normal period for these treatment-seeking women and what amount of blood loss they are willing to accept after treatment. Second, we should consider redefining the HMB criteria and involving a patient-centred definition of heavy menstrual bleeding.

Should we still use the Pictorial Blood Assessment Chart?

Higham et al. developed a subjective method to determine whether or not women meet the diagnosis of HMB: the Pictorial Blood Assessment Chart (PBAC). The self-assessed PBAC consists of diagrams representing different soiled towels and tampons. Women are instructed to count their number of used towels or tampons each day and then divide them by the level of soiling. The chart is scored using the scoring system devised by Higham et al. This measurement method has a specificity and sensitivity of 80-90% when compared to the gold standard. Higham et al. found that a PBAC score of >100 correlated with 80mL blood loss. Janssen et al. recommended a cut-off score of 185 and Zakherah a cut-off point of 150 points for the definition of HMB. A PBAC score of >150 points is most often used as an inclusion criterion in HMB studies. In all of these studies the definition of HMB is based on blood loss of 80mL or on anaemia. Thus, if we question the 80mL threshold, we should also question the definition of HMB measured by PBAC. Nevertheless, the PBAC could provide insight into a woman's complaints regarding menstrual bleeding problems. Clinicians must take into account and inform their patients of the fact that there is a wide variation in menstrual cycles and menstrual bleeding between women. This variation should be discussed with the patient as this knowledge can sometimes be reassuring for women.

In addition to its use for diagnostic purposes, the PBAC is also used as an outcome measurement tool in many studies. This is remarkable because it had never been

evaluated for this purpose. We perform this evaluation in chapter 7. We found an association and high accuracy between (decrease in) PBAC score after treatment and satisfaction or re-intervention. Therefore the PBAC seems to be a promising tool for evaluating treatment effects. Our study indicates that a low PBAC score or a decrease of at least 80% may be a valuable endpoint in HMB studies. Future studies should validate the use of the PBAC score after treatment.

What outcome measure should we use?

As described in chapter 8 not only the PBAC, but many different primary outcomes are used to evaluate the effects of different treatment options for HMB. Endpoints and measurement tools differ from publication to publication. Literature on HMB treatment is therefore hard to compare. There should be more uniformity, but on what aspect should we focus? Should HMB be studied using objective assessments with alkalin measurement, menstrual diaries or subjective assessments such as satisfaction or (disease specific) QoL? Currently there is no standardised outcome that can be used to evaluate the effects of treatment for HMB.

For evaluating the effects of a (new) treatment we need objective parameters on the effectiveness, side effects and burden of these treatments. When counselling patients regarding a treatment, the clinician must ensure their patients are well informed about these results. Only then can women make a deliberate choice. This does not imply that we should omit subjective outcomes. Of course clinicians want their patients to be satisfied and have better QoL; however, power calculations should not be based on subjective outcomes. Subjective outcomes are the result of more factors than the treatment effect alone. Expectations and coping play a role as well and clinicians should counsel each patient in order to find *her* appropriate treatment. Thus by knowing the objective parameters and counselling the patient about these parameters, the clinician can help the patient decide for herself what she prefers. Of course, it is still very interesting to study satisfaction and QoL, but only as secondary outcomes. A satisfaction scale or QoL questionnaire must be developed for researchers to use in their studies. Only then will they be able to compare or pool this type of data on a larger scale (individual patient data analyses).

In conclusion, it would be much easier, but also much more objective if all trials of HMB would be performed with the same outcome measures. An international panel of experts should develop core outcome sets and determine how clinically important outcomes can be selected and standardised .

Body Mass Index (BMI) as a prognostic value for endometrial ablation?

Many endometrial ablation techniques have been evaluated as a treatment for heavy menstrual bleeding and nowadays these techniques are widely implemented. Endometrial ablation seems to be an effective procedure with high success rates. In order to counsel patients correctly, clinicians should recognise prognostic (un)favourable parameters. Therefore, knowledge of factors that affect the success rate of endometrial ablation will enable patients to make the best choice regarding treatment. Obesity and overweight is one of the most common health issues nowadays, and thus it is very important to gain more information about its effect on HMB treatment effectiveness. Women with a higher body mass index (BMI) are more likely to have heavier periods than women with a lower BMI. Obese women tend to have a greater ability to regenerate endometrial tissue. Because their aromatase system and extraovarian steroidegenesis are often not inhibited by traditional medical therapies, obese women tend to be more difficult to treat. Hysterectomy is the definitive treatment for such patients; however, obesity is often associated with comorbidities that significantly increase perioperative morbidity. These comorbidities include cardiovascular disease, respiratory compromise, insulin resistance and type 2 diabetes mellitus, infection, and thromboembolism. Furthermore, surgery in obese women is often technically challenging. Endometrial ablation could reduce the need for hysterectomy and its associated perioperative morbidity among women with obesity. Endometrial ablation is a safer option for this group of women but it is unclear if obesity is also an independent risk factor for postablation outcomes. Three trials published conflicting outcomes, as two showed no correlation between BMI and success of endometrial ablation, while one study showed a negative correlation between BMI and satisfaction.[18,19,22] Limitations of the previous publications are either their small sample size or their retrospective nature, which did not allow for standardised diagnosis and outcome measures. More evidence is needed to determine which factors influence the success rate of endometrial ablation and special attention should be paid to patients' body mass index. Combining individual patient data (IPD) from randomised trials can play an important role in this investigation.

In conclusion, my suggestions for future research are:

- Conduct the MIRA-trial to determine whether LNG-IUS or endometrial ablation is more (cost-) effective in the treatment of HMB.
- Redefine the HMB criteria; involve a patient-centred definition for heavy menstrual bleeding.
- Study patient preferences regarding the amount of blood loss after treatment.
- Validate the PBAC score as an outcome parameter.
- Study PBAC as a predictive value for treatment outcome.
- Develop core outcome sets in HMB research.
- Use IPD to evaluate prognostic factors that affect the success/failure of endometrial ablation.

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CHAPTER 11

Valorisation addendum

Why is this thesis relevant?

The treatment of heavy menstrual bleeding (HMB) has been studied for many years as several different techniques and medical treatments have been developed. Clinicians are looking for a treatment that suits the complaints and preferences of the women affected by this condition. The studies presented in this thesis focus on the effectiveness of different treatments. We also explored patient preferences and questioned the outcome measures currently used for HMB studies.

Relevance

About 30-50% of all menstruating women report that their periods are (very) heavy, and of these women 25% report that their periods are a marked or severe problem. Heavy menstrual bleeding is the most important reason for a visit at the outpatient department of gynaecology and each year one in 20 women between 30 to 49 years of age consult their general practitioner (GP) with this complaint. HMB has attracted so much medical attention because it is a major health problem and has a significant impact on the medical, social, and psychological well-being of women. Therefore, there is a need for effective (diagnostic) strategies and treatment modalities.

It must be determined what entails a normal period for these treatment-seeking women and what amount of blood loss they are willing to accept after treatment. Only then we can study effectiveness.

Because of its high prevalence, an optimal treatment for HMB is of utmost importance. Usual care in The Netherlands implies two strategies for the treatment of heavy menstrual bleeding if drug therapy fails: first, there is the levonorgestrel intrauterine system (LNG-IUS) that can be applied easily by the GP, which saves costs, but has considerable failure rates. As an alternative, endometrial ablation is also very effective, but this treatment is more invasive and has to be performed by a gynecologist. Large randomised controlled trials comparing LNG-IUS with endometrial ablation are lacking and hence no preferred advice for the use of one of these treatment possibilities is available. When we estimate that treatment for heavy menstrual bleeding involves many women annually, there can be a potential saving from implementing the best strategy. Therefore, a direct comparison of both strategies on cost-effectiveness is essential to determine which strategy should be advocated.

Finally, we found that there is no standardized outcome to define the effect of treatment for HMB and a variety of primary outcomes are currently used. For the interpretation of data it is important that there is consistency in the choice and definitions in primary and secondary outcomes. Only then clinicians can give their patients well-founded advice.

Target groups

The results of this thesis are interesting for clinicians (both gynecologists and general practitioners), patients and treatment developers (industry). Together we need to determine what the best course of treatment is.

The choice for a treatment depends on the known effectiveness rates, experiences and patient preferences. The results presented in this thesis on the effectiveness of the minimally invasive options (endometrial ablation), and patients' preferences will contribute to further improvement of patient counselling and development of guidelines and would therefore hopefully lead to an increase in patient satisfaction. The industry should also focus on our data of effectiveness and preferences since their aim is also to offer patients a desirable and long-term solution for HMB.

Activities and Innovation

Our results have been published in scientific research journals and were discussed on gynecological congresses. Besides, this thesis consists of co-working between national and international experts in the field of HMB resulting in more knowledge and more research opportunities.

In the Netherlands, we initiated a multicenter randomised controlled trial (RCT) comparing LNG-IUS and endometrial ablation; the MIRA trial. A RCT that is organised in a network infrastructure in which both GP's and gynecologists collaborate. It has got the largest study population compared with other trials and has a long term follow-up of 2 years. Due to its study design and outcome measures, the results will be applicable for a large group of women suffering from heavy menstrual bleeding.

Due to the opportunity to work with a large individual patient data (IPD) cohort, we were able to study outcome parameters on a large scale, of which the Pictorial Blood Assessment Chart score is presented in this thesis. This co-working also laid the basis for developing the review of the chosen primary outcomes. We noticed the difference in chosen and reported outcomes among the different papers and

decided to create more awareness about what we are actually studying globally. It is alarming that there is so little consistence in the measurements and chosen outcomes in these HMB trials.

Schedule and implementation

It must be determined what entails a normal period for treatment-seeking women and what amount of blood loss they are willing to accept after treatment. The Pictorial Blood Assessment Chart must be validated as an outcome measure and we should also study patients preferences regarding blood loss. Then, we should consider redefining the HMB criteria and involve the patient-centred definition of HMB. Besides, an international panel of experts must develop core outcome sets and determine how clinically important outcomes can be selected and standardized.

In order to evaluate treatments, predict their effectiveness and inform patients about these predictions, adequate follow-up of these therapeutic interventions is still needed for good evidence-based clinical decision making. So long term follow-up, as published in chapter 3 and 4, but also the proposed MIRA trial are examples for this. The result of these trials are of great importance for the development of guidelines and decision aids. Implementation of the outcome of the MIRA trial in daily practice seems highly feasible since general practitioners and gynaecologists performed this trial.

DANKWOORD

CURRICULUM VITAE

Dankwoord

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Curriculum Vitae

Malou Herman werd geboren op 18 september 1987 te 's-Hertogenbosch. Zij behaalde haar gymnasiumdiploma in 2005 aan het Stedelijk Gymnasium te s-Hertogenbosch. Hetzelfde jaar startte zij met de opleiding geneeskunde aan de Universiteit Maastricht en in juni 2011 behaalde zij haar artsexamen. Hierna werkte zij als ANIOS gynaecologie&obstetrie in het Maxima Medisch Centrum Veldhoven en kreeg zij tevens de aanstelling als arts onderzoeker binnen het consortium gynaecologie en obstetrie. Tijdens deze aanstelling heeft Malou onder leiding van prof. dr. Marlies Bongers en prof.dr. Ben Willem Mol de MIRA studie, een multicentrum studie, opgestart en de basis van haar proefschrift gelegd. 1 januari 2013 begon Malou aan de opleiding tot gynaecoloog in het Maxima Medisch Centrum Veldhoven (opleiders prof.dr. M.Y. Bongers en dr. J.W. Maas). Sinds januari 2014 volgt zij haar 2e en 3e opleidingsjaar in het Universitair Medisch Centrum Maastricht (opleiders prof.dr.R.F. Kruitwagen en dr. G.A.Dunselman). Malou Herman woont samen met Niels Verweij in 's-Hertogenbosch.

Malou Herman was born on the 18th of September 1987 in 's-Hertogenbosch, the Netherlands. After finishing secondary school at the Stedelijk Gymnasium in 's-Hertogenbosch in 2005, she started her medical study at Maastricht University. In 2011 she graduated from medical school. She worked as a resident at the department of Obstetrics and Gynaecology at the Maxima Medical Center in Veldhoven, the Netherlands. In the same year she became a researcher at the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology. During this period, she started a multicenter study, the MIRA, headed by prof. dr. Marlies Bongers and Prof. Ben Willem Mol, and laid the foundation of her thesis . She started her specialist training at the Maxima Medical Center, Veldhoven, the Netherlands on the first of January 2013 (supervisors prof.dr. M.Y. Bongers and dr. J.W. Maas). Her second and third training years are followed at the University Medical Center in Maastricht, the Netherlands (supervisors prof. dr. R.F. Kruitwagen, dr. G.A. Dunselman).
Malou Herman lives together with Niels Verweij in 's-Hertogenbosch.

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