Management of heavy menstrual bleeding

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Chapter 9

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

This thesis focuses on the treatment of heavy menstrual bleeding (HMB), both in general practice and at the gynaecology department. We focus in particular on two of the treatment options, namely the levonorgestrel intrauterine system (LNG-IUS) and endometrial ablation, which are both known to be effective for the treatment of HMB. These interventions clearly differ in treatment characteristics, where the LNG-IUS is less invasive than endometrial ablation, reversible and can be easily placed in primary care. We do not know which treatment is most effective and which treatment women with HMB prefer. We compared both treatments in a randomised controlled trial (RCT). Our aim was to investigate if a treatment strategy starting with the LNG-IUS was noninferior to a treatment strategy starting with second generation endometrial ablation. Alongside this clinical trial, we investigated the cost-effectiveness of both treatment strategies. To optimise the individual counselling of a woman with HMB, we explored which treatment characteristics are important in a woman's preference for one or the other treatment option. We also explored if treatment success of the LNG-IUS and endometrial ablation was different for a subgroup of women with low coagulation factor levels.

SUMMARY OF MAIN FINDINGS

In **chapter 2** we analysed data of the Registration Network Groningen (approximately 30 000 registered patients per year) to investigate how many women consulted their general practitioner (GP) with symptoms of HMB between 2004 and 2013. We included 881 women with newly diagnosed HMB in our cohort. We found a mean annual incidence of 9.3 per 1000 person years (95% confidence interval: 8.5–10.2) with a peak incidence among women aged 35-54 years (up to 14.3 per 1000 person years). Most women received hormonal treatment (46%) within three months after diagnosis, but just as large a group (44%) received no medication at all. The LNG-IUS was prescribed in 2.4% of the women. In 2008, the Dutch General Practice guideline on Vaginal bleeding was revised to recommend the LNG-IUS as a first-choice treatment for HMB, but we saw no significant increase in the number of LNG-IUS prescriptions for HMB over time. At six months after

diagnosis, 13% of the women switched to a second treatment. Women were referred to a gynaecologist in 18% of cases, mainly within one year of diagnosis.

In **chapter 4** we present the results of a multicentre RCT with a noninferiority design comparing a strategy starting with the LNG-IUS (Mirena®) with a strategy starting with endometrial ablation (Novasure®) for the treatment of HMB (MIRA trial). In total 270 women with HMB and a Pictorial Blood Assessment Chart (PBAC) score exceeding 150 points, aged 34 and older, without a pregnancy wish or intracavitary pathology, were randomised between a strategy starting with the LNG-IUS and a strategy starting with endometrial ablation. Women were recruited at gynaecology departments and general practices in the Netherlands. The primary outcome was blood loss at 24 months after randomisation, measured with the PBAC-score. The noninferiority margin was set at 25 PBAC-points. This margin is the maximum difference between the treatments that we are willing to accept before declaring them different in effectiveness. Secondary outcomes included reintervention rates, controlled bleeding rates (PBAC ≤75), patient satisfaction, disease specific and generic quality of life and sexual function. Mean PBAC-scores at 24 months were 65 in the LNG-IUS group (N=132) and 14 in the EA group (N=138). The mean difference between the groups was 51 points (95% CI 4.3 to 96.7, p = 0.87). The 95% confidence interval overlapped the predetermined noninferiority margin of 25 points, meaning we were unable to demonstrate noninferiority nor inferiority of the LNG-IUS strategy regarding menstrual blood loss.

Although the mean PBAC-score was lower in the endometrial ablation group, the rates of controlled bleeding were high in both groups. The PBAC-score had decreased to ≤75 points in 87% of women in the LNG-IUS group and 94% of women in the endometrial ablation group (RR 0.93, 95% CI 0.85 to 1.01, p = 0.06). There were no significant differences between the two treatment strategies on the secondary outcomes patient satisfaction, disease specific quality of life and sexual function. In the LNG-IUS group 74% of women were satisfied with the treatment effect versus 84% in de endometrial ablation group (RR 0.88, 95% CI 0.76 to 1.01, p = 0.06). Women who started with the LNG-IUS were more likely to receive a reintervention (35%) compared to women who started with endometrial ablation (20%) (RR 1.77, 95% CI 1.17 to 2.68, p = 0.006). This difference was mainly caused by 24% of the women in the LNG-IUS group receiving endometrial ablation as a surgical reintervention. Furthermore, 15% of women in the

LNG-IUS group received medication as a reintervention compared to 9.4% in the endometrial ablation group. The hysterectomy rate in both groups did not differ significantly: 7.1% in the LNG-IUS group and 10% in the endometrial ablation group (RR 0.70, 95% CI 0.31 to 1.56, p = 0.38).

In **Chapter 5** we evaluated the cost-effectiveness of the LNG-IUS strategy versus the endometrial ablation strategy from a societal perspective over a 24 months' time horizon. We calculated direct medical costs (costs of the intervention, reinterventions, hospital admission and home care) and (in)direct non-medical costs such as work absenteeism, for both strategies. The primary outcome for the cost-effectiveness analysis was menstrual blood loss at 24 months, measured with the mean PBAC-score and a secondary outcome was the proportion of women with controlled bleeding (PBAC-score ≤ 75 points).

LNG-IUS insertion was mostly performed by the gynaecologist at the outpatient department (89%) and in 3.3% by the gynaecologist in the operating room. In 7.4% of the cases the LNG-IUS insertion was performed by the GP. Endometrial ablation was performed by the gynaecologist in the operating room in 58% of the cases and at the outpatient department in 42% of cases. Total costs after 24 months were €2,285 in the LNG-IUS group and €3,465 in the endometrial ablation group (mean cost difference -€1,180, 95% CI -€2,097 to -€1,111). The incremental cost-effectiveness ratio (ICER) was €23 (95% CI €5 to €111) per PBAC-point indicating that endometrial ablation costs €23 per additional PBAC-point reduction of menstrual blood loss as compared to the LNG-IUS. A sensitivity analysis under the assumption that all LNG-IUS insertions were performed in primary care increased the ICER to €28 per PBAC-point. Expressed as the percentage of women with controlled bleeding, the ICER was €169 per 1% additional success rate for endometrial ablation compared to the LNG-IUS.
The strategy starting with the LNG-IUS was cheaper than the strategy starting with endometrial ablation but slightly less effective. Offering the LNG-IUS more often in primary care will further reduce costs. Performing endometrial ablation as an office procedure may be another possibility to reduce costs of HMB treatment.

Of the 645 women who were eligible for the RCT, 270 women gave informed consent for participation in the MIRA trial. In a large proportion of the women who did not want to participate, treatment preference played a role. In **chapter 6** we investigated in a

consecutive sample of women presenting with HMB in general practice or at the gynaecology outpatient department what their preferences were regarding treatment characteristics of the LNG-IUS and endometrial ablation. Women were asked to complete a questionnaire (discrete choice experiment) with 16 choice sets with varying levels of characteristics of the LNG-IUS or endometrial ablation to assess the relative importance of the characteristics and the trade-offs that women make between them. Characteristics included procedure performed by gynaecologist or GP; reversibility of the procedure; probability of dysmenorrhea; probability of irregular bleeding; additional use of contraception; need to repeat the procedure after five years; and treatment containing hormones. 165 women completed the questionnaire. The characteristic found most important was whether a treatment contains hormones. Women generally preferred a treatment without hormones, a treatment with the least side effects, and no need for a repeat procedure or additional contraception. Women completing the questionnaire at the gynaecology outpatient department preferred a definitive treatment to be performed by a gynaecologist in contrast to women in primary care, who did not indicate a specific preference.

In women with HMB, there is an increased prevalence of coagulation factor deficiencies. It is unknown whether coagulation factor levels influence HMB treatment success. In chapter 7 we asked women participating in the MIRA trial separate informed consent to measure coagulation factor XI (FXI) and Von Willebrand Factor (VWF) levels and investigated if coagulation factor levels were associated with the effectiveness of the LNG-IUS and endometrial ablation. We defined treatment success as a PBAC-score ≤75 points without a surgical reintervention. We divided the FXI and VWF levels in categories below and above the median and performed a logistic regression analysis. Ninety-five women gave informed consent and 93 women could be analysed. Decreased FXI and VWF levels were found in 1.1% and 3.2%, respectively. We found that endometrial ablation was less effective in women with FXI levels below the median compared to women with FXI levels above the median (OR 0.08, 95% CI 0.01 to 0.68). For the LNG-IUS, there was no difference in treatment success between higher and lower FXI levels. Furthermore, there were no differences in treatment success between higher and lower VWF levels in both treatment groups. The MIRA study was not powered to perform this analysis, therefore our findings can only be seen as explorative. Our findings do not

change current HMB treatment recommendations for women with decreased coagulation factor levels: for the time being, they should be offered the same treatment options as other women with HMB.

For successful completion of a clinical trial, we depend on patients who are willing to participate in a clinical trial. In addition, the clinician (in the MIRA trial: the GP or gynaecologist) is a key link in the recruitment of patients for clinical trials. In **Chapter 8** we interviewed 16 participating GPs in the MIRA trial to identify barriers and facilitators for patient recruitment. The incidence of the disease under study, awareness of the study, attitude towards scientific research, perceived burden for the patient, usual care by the GP, time investment, characteristics of the GP and their practice, and patient experience of research participation were identified as factors that influence patient recruitment. It is important that study procedures are clear, requiring limited (time) investment from the GP, and that researchers invest in personal communication and reminders. We believe that placing greater importance on scientific research during the GP training programme could also serve as a means to motivate future GPs to integrate scientific research in their clinical practice.

GENERAL DISCUSSION

This study was designed to find answers to some important outstanding issues regarding the optimal treatment of HMB. International HMB treatment guidelines recommend several first-line options, including the combined oral contraceptive pill (OCP), oral progestogens, nonsteroidal anti-inflammatory drugs (NSAIDs) and tranexamic acid.[1-4] Treatment choice depends on patient preference for hormonal or non-hormonal treatment and on the medication's characteristics. When oral medication fails or is undesired, more invasive treatment options, such as the LNG-IUS or endometrial ablation or eventually, hysterectomy, are available. The LNG-IUS has been proven superior to oral medication in the treatment of HMB.[5,6] No studies have been published that directly compare oral medication to second generation endometrial ablation. Considering the comparison of the LNG-IUS and endometrial ablation, one Cochrane systematic review and one meta-analysis of individual participant data (IPD-MA) had compared the LNG-IUS to second generation thermal balloon ablation at the start of the MIRA trial in 2012.[7,8] None of the included studies had compared LNG-IUS with bipolar radiofrequency ablation. The six RCTs included in the Cochrane review showed inconsistent results for a difference in the amount of menstrual blood loss (measured with the PBAC) between interventions.[9-14] Some studies showed that endometrial ablation was significantly more effective than LNG-IUS in controlling bleeding at one year, but in other studies the LNG-IUS was more effective or no significant difference was found between the interventions. No significant differences were found in quality of life scores and satisfaction rates between LNG-IUS and endometrial ablation. The review authors concluded further comparative research is required because of weak, inconsistent evidence of one intervention being superior to another. The IPD-MA found no significant differences in PBAC-scores changes, amenorrhea, satisfaction rates, quality of life, or hysterectomy rates between the LNG-IUS and endometrial ablation. The results of these two reviews must be interpreted with caution, as the majority of the included studies suffered from deficiencies, with a high risk of attrition bias, small sample sizes and relatively short follow-up periods (ranging from 6-12 months). During the conduction of the MIRA trial, two other RCTs were performed that compared the LNG-IUS to second generation endometrial ablation.[15,16] One study comparing thermal

balloon ablation to the LNG-IUS showed higher satisfaction and lower treatment failure after five years in favour of the LNG-IUS.[15] The other trial concluded that bipolar radiofrequency ablation was superior to the LNG-IUS in terms of satisfaction and amenorrhea.[16] Both trials had small intervention groups and their conflicting results add to the uncertainty which treatment is most effective.

Randomised controlled trials comparing bipolar radiofrequency with thermal balloon endometrial ablation showed higher rates of amenorrhea and shorter procedural time for the bipolar radiofrequency endometrial ablation.[17-19]

From the results of the already conducted trials, it is unclear which intervention (LNG-IUS or endometrial ablation) is most effective for the treatment of HMB. The studies had multiple limitations and due to the inconsistent results, the LNG-IUS and ablation could also be equally effective. Because of the advantages of the LNG-IUS over endometrial ablation in terms of invasiveness, reversibility, contraceptive effect, and feasibility in general practice, we investigated if a strategy starting with the LNG-IUS is noninferior to a strategy starting with bipolar radiofrequency endometrial ablation. We performed a large multicentre noninferiority RCT with a relatively long follow-up period of 24 months and we enrolled both primary and secondary care patients. We compared the LNG-IUS to bipolar radiofrequency endometrial ablation, because the latter is a frequently used second generation ablation technique and studies directly comparing this treatment with the LNG-IUS are scarce. We chose to measure multiple outcomes, including satisfaction, quality of life, reinterventions and as our primary outcome the amount of blood loss, measured with the PBAC, to add relevant information to the existing evidence in the field of HMB treatment. We found in the MIRA trial that both the LNG-IUS and bipolar radiofrequency ablation were effective in reducing menstrual blood loss in the majority of women (PBAC-score ≤75 points), though a higher mean PBAC-score was observed in the LNG-IUS group. Noninferiority of a strategy starting with LNG-IUS could not be demonstrated. Therefore, it remains uncertain whether the LNG-IUS is equivalent or inferior to endometrial ablation in reducing the amount of blood loss. The majority of women in both groups were satisfied with the result of the treatment strategy and no significant differences over time were found in disease specific quality of life and sexual function between the two treatment groups. However, the desired treatment effect was

more quickly achieved and the number of reinterventions was lower in the endometrial group.

Clinical implications of our findings

In our registration data from primary care, we found that in the majority of women with HMB in primary care, an expectant policy or oral medication was chosen. The LNG-IUS was started in only 2.4% of women and less than one in five women were referred to secondary care. These observations suggest that conservative treatment is sufficient in most women. However, we do not know whether this strategy was actually satisfactory for these women. For example, it is conceivable that they did not revisit their GP because they were not familiar with other treatment options. While the LNG-IUS or endometrial ablation are recommended alternatives for women in need of further treatment. Because the LNG-IUS has several advantages compared to endometrial ablation, including the less invasive and reversible nature of the procedure, costs, and feasibility in general practice, we aimed to investigate if starting with the LNG-IUS is noninferior compared to endometrial ablation in the treatment of HMB. If the LNG-IUS would perform equivalent or even better than endometrial ablation (in other words: not inferior), these advantages of the LNG-IUS would justify a physician to advise the LNG-IUS as first treatment, providing good quality care as close to the patient as possible.
In the MIRA trial, we could not demonstrate noninferiority nor inferiority of the LNG-IUS strategy in terms of the amount of menstrual blood loss. The difference in mean PBAC-scores at 24 months was 51 points, comparable to five maximum saturated tampons (or 2,5 maxi pads) per menstrual period. However, the chance of successful blood loss reduction (PBAC-score ≤75 points) did not differ significantly between the treatments (87% versus 94% in the LNG-IUS versus endometrial ablation strategy). These percentages might be easier to interpret for a woman with HMB than the amount of blood loss after treatment expressed in mean PBAC-scores, and can be used when counselling women about the relative effectiveness of both treatments.
Furthermore, other treatment outcomes should be considered as well when advising on which treatment to choose. In addition to the amount of blood loss, the impact of HMB on daily life is an important outcome.[2] We saw no significant differences in satisfaction and in disease specific quality of life or sexual function over time between the two

treatment strategies. These results are in line with the summarised evidence from other studies.[20] The LNG-IUS and endometrial ablation differed in terms of reintervention risk and (speed of) achieving the desired amount of blood loss reduction. Other treatment characteristics can be decisive in the choice of the LNG-IUS or endometrial ablation. In our preference study (chapter 6), we showed that whether the treatment contains hormones is the most important characteristic influencing treatment choice. The fact that the LNG-IUS releases a progesterone, the risk of a common side effect of the treatment (spotting), or the risk of needing an additional intervention (replacement of the LNG-IUS after five years or another treatment for HMB) can all be reasons for opting for endometrial ablation instead of the LNG-IUS.

The characteristics and outcomes that are decisive in the treatment choice are probably not the same for every woman. Lacking consistent and valid evidence for a clinically relevant superiority of an intervention, it is important as a physician to outline the complete picture. Only then can a woman make a well-considered choice for herself. The results of our study can be used in shared decision making for women suffering from HMB. The advantages of endometrial ablation are a better chance of reaching the desired effect faster and with a lower risk of additional interventions. These should be weighed against the advantages of the LNG-IUS, which is a less invasive and reversible treatment with a contraceptive effect, feasible in primary care. Moreover, the fact that a strategy starting with the LNG-IUS is cheaper than starting with endometrial ablation may also play a role for healthcare providers and policymakers in deciding which treatment to offer first.

Generalisability of our study results

We performed a pragmatic trial with the aim to include patients comparable to the patients in daily practice of GP and gynaecologist who would opt for either the LNG-IUS or endometrial ablation. Despite our efforts to recruit patients in both general practice and gynaecology departments, only a small proportion of patients were recruited in general practice, in the MIRA trial (chapter 4 and 5) as well as in the preference study (chapter 6). The small proportion of patients recruited in general practice may influence the generalisability of the MIRA trial results, because women referred to secondary care may have more severe blood loss or a longer duration of HMB. In the MIRA trial, however,

we found that it was not the duration of symptoms nor the amount of menstrual blood loss, but rather the local referral policy and the possibility to perform diagnostic tests (such as first-line transvaginal ultrasonography) determined whether a woman was recruited by the GP or the gynaecologist. We therefore think that the women included in this pragmatic trial, recruited from multiple regions in the Netherlands, fairly well reflect women with HMB in daily practice that opt for the LNG-IUS or endometrial ablation. The results of our study are generalizable to women without a strong treatment preference and without a future child wish, for whom oral medication was not desirable or not successful.

It should be noted that these women are only a subgroup of all women presenting with HMB in primary care. The results from our registration data from primary care (chapter 2) support this hypothesis, as we saw that in a substantial proportion of women with HMB (44%) no medication was initially started and less than one in five women were referred to secondary care.

Although we think that the results of the MIRA trial can be applied to the target group with HMB in daily practice, we do have indications that the patient preference may differ between women in general practice versus women at the gynaecology outpatient department. We saw in chapter 6 that a majority of patients in secondary care had a preference for a definitive solution for HMB, performed by the gynaecologist. Women recruited in general practice did not have a clear preference for these characteristics. We expect that in primary care, there may be a larger proportion of women with a preference for a more conservative treatment than in secondary care.

The setting where the LNG-IUS treatment is performed did influence the results of our cost-effectiveness analysis (Chapter 5), because the costs of LNG-IUS insertion differ between primary and secondary care. We therefore added a sensitivity analysis with the assumption that all LNG-IUS insertions were performed in primary care. We demonstrated that performing the LNG-IUS insertion in primary care will reduce costs of HMB treatment and thereby increases the likelihood that the LNG-IUS is cost effective.

Methodological considerations

Interpretation of the noninferiority design and margin

All the previous evidence about the effectiveness of the LNG-IUS versus endometrial ablation came from RCTs with a superiority design and was inconclusive. Since the LNG-IUS has several advantages compared to endometrial ablation, we did not aim to prove superiority of the LNG-IUS but rather investigate whether the LNG-IUS is no worse (noninferior) than endometrial ablation. But when do we decide that the LNG-IUS is not inferior to endometrial ablation? In other words: what should be our noninferiority margin? We chose the PBAC-score as our primary outcome and previous studies have shown that a difference of 50 PBAC points represents a clinically meaningful difference.[10,12,21]. The difference between the two treatments should be smaller than a clinically relevant difference. In order to minimise the chance that we would wrongly demonstrate noninferiority, we opted for a conservative noninferiority margin of 25 points.

Unexpectedly, the distribution of the PBAC-scores showed a much wider spread than we had estimated in advance on the basis of the available literature, the upper limit of the 95% confidence interval of the mean difference in PBAC-score well exceeded the 25-point margin (see figure 1).

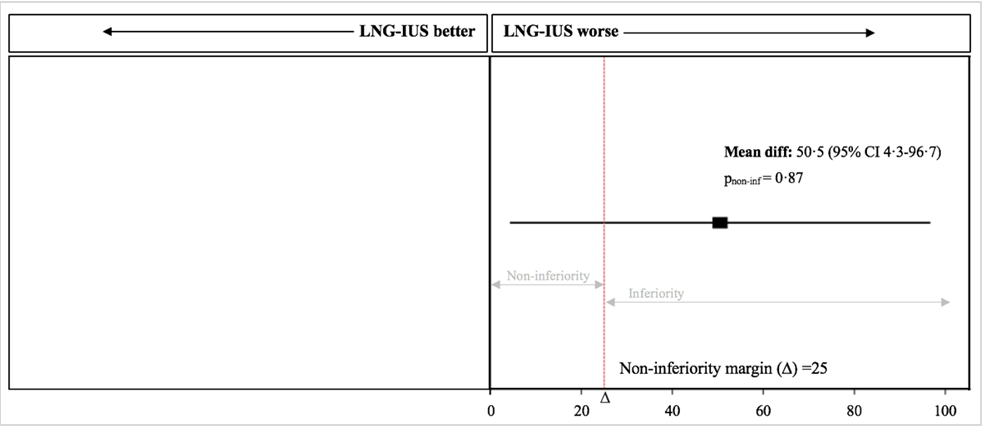

Figure 1. Difference in mean PBAC-score at 24 months follow-up

LNG-IUS: levonorgestrel-releasing intrauterine system. LNG-IUS compared to endometrial ablation. Confidence interval determined using bootstrapping (2.5th and 97.5th percentile).

The mean difference in PBAC-score was in favour of endometrial ablation. But due to the broad 95% confidence interval, the results of our study were inconclusive: We could not conclude whether the LNG-IUS is inferior or not inferior to endometrial ablation (see Figure 1).

The majority of women in both the LNG-IUS and the endometrial ablation group had a robust decline in PBAC-score with successful blood loss reduction in 87% and 94% of women respectively (PBAC-score ≤75). In the LNG-IUS group in particular, there were outliers with PBAC-scores exceeding 750 points. These outliers, in which treatment failed, mainly caused the large spread in the PBAC-score. A possible explanation for the broader confidence interval found compared to other studies is that some of these studies had a high risk of attrition bias. It seems that (some of) the women with a high PBAC-score after treatment were lost to follow-up and/or not included in the analyses of previous studies.[9,10,12] A strength of our trial was the high follow-up rate, with only 9% of the primary outcome missing at 24 months of follow-up.

Statistical challenges: distribution of the primary outcome

A major challenge in our analysis was the non-normal distribution of our primary outcome, the PBAC-score. We based our power analysis and mean outcome estimates on previous superiority studies where PBAC-scores were presented as means and the t-test statistic was used for the primary analysis, assuming a normal distribution of the data. Some studies presented the estimate of the PBAC-scores in medians, but those studies had much smaller sample sizes than our trial. The PBAC-scores at 24 months follow-up in our trial had a highly skewed distribution, with a large proportion of PBAC-scores with a value of zero. A zero-inflated negative-binomial model to evaluate a difference in the primary outcome measure would better fit the data. However, the noninferiority design of the study precluded changing the analysis of the primary outcome as the noninferiority margin was defined in terms of a mean difference between the treatment groups. Therefore, we estimated the mean difference and calculated confidence intervals using bootstrapping and also relied on bootstrapping to test the noninferiority hypothesis. We added the zero-inflated negative-binomial model as a secondary analysis. A possible explanation that our data was more skewed than expected is that we compared two strategies rather than the effect of the interventions

itself. In these strategies, women were allowed to undergo a reintervention, which made them eventually more likely to achieve a PBAC-score of zero. In some of the previous studies, women with treatment failures (including women requiring a hysterectomy) were excluded from the analyses and/or were lost to follow-up.[9,10,12]

Which outcome measure to choose for HMB?

Menstrual blood loss-related outcomes are the most frequently used primary outcome in HMB studies, with most studies focusing on amenorrhea.[22] However, amenorrhea is not necessarily the most important outcome for women with HMB. Clinical HMB guidelines nowadays focus more on the impact of menstrual blood loss on daily life than on the objective amount of blood loss when defining HMB.[1,23] Patient satisfaction and quality of life are both being recognized as important patient-oriented outcomes in HMB, as they better reflect the needs of women.[24] The NICE guideline on HMB emphasises that any treatment for HMB should aim to improve a woman's quality of life rather than focusing on blood loss.[2] Disease-specific quality of life instruments should be preferred above generic quality of life instruments, because HMB symptoms are cyclic and not constant over time and symptoms are disturbing but not necessarily affecting all domains covered in a generic instrument such as the SF-36.[25] In accordance with these guidelines we considered to choose (disease specific) quality of life as the primary outcome. However, there is no consensus on the minimum clinically relevant difference in MMAS (Menorrhagia Multi-Attribute Scale) score and thus this outcome measure would be difficult to apply in our noninferiority design. We initially choose another subjective primary outcome: patient satisfaction with the treatment strategy. However, patient satisfaction is dependent on patient's expectation and experiences with previous treatment results. Our Methodology Advisory Board recommended opting for the amount of blood loss as the primary outcome, measured with the PBAC-score. The PBAC is the most frequently used instrument to assess the amount of menstrual blood loss and the PBAC-score is found to be associated with satisfaction and reintervention rates.[26] We measured multiple objective and subjective outcomes in the MIRA trial. There is much heterogeneity in the outcomes used in studies evaluating the treatment of HMB. This variability undermines the interpretation of data and consistent synthesis of evidence in systematic reviews. It is internationally recognized that a standardised

collection of outcomes – a 'core outcomes set' is needed.[22,27] In addition to systematically reviewing the literature to identify potential outcomes, it is important that all stakeholders (healthcare providers, patients, grant providers, researchers) are involved in the choice of the core outcome set. An initiative is currently running to develop such a core outcome set for HMB.[28]

Future directions

Pathophysiology HMB

Although it is assumed that a different endometrial haemostasis plays a role in essential HMB, the pathophysiology of HMB is not fully elucidated yet. And relatively little is known about the pathophysiology of HMB in relation to myomas, polyps and adenomyosis. This is also noted as a knowledge gap by the Dutch Society of Obstetrics and Gynaecology (NVOG).[23] More information about the causal relation between myomas, polyps or adenomyosis and HMB will help us decide whether these women need specific treatment or can be treated the same as women with essential HMB. A better understanding of the pathophysiology of HMB can give us direction towards possible new treatment targets for HMB.

In a subgroup of women with HMB a coagulation disorder plays a role. In chapter 7 we performed an explorative study on the influence of coagulation factor levels on HMB treatment success. In this study, it seemed that endometrial ablation was less effective in women with lower FXI levels compared to women with higher FXI levels. We did not find this difference in treatment success in the LNG-IUS group or for different VWF levels. Increased fibrinolysis can be thought of as a possible mechanism, but we don't have a clear explanation why this difference in treatment success would only be seen with endometrial ablation and not with the LNG-IUS. Ideally, we would repeat this analysis in another, larger cohort of women with HMB to test whether the results from our study are being confirmed and whether this difference is clinically relevant. Data from women with HMB from other trials could be used, with additional informed consent to collect blood samples for coagulation factor analyses.

Patient preferences

The discrete choice experiment we performed (Chapter 6) showed that whether a treatment contains hormones was the most important characteristic influencing treatment choice. Other characteristics included in the model were: procedure performed by gynaecologist or GP; reversibility of the procedure; probability of side effects (dysmenorrhea, irregular bleeding); additional need for contraception and need to repeat the procedure after five years. The choice of these characteristics was based on literature, expert opinion and patient interviews. With the information gathered from the MIRA trial, it is interesting to re-consider these attributes. For instance the risk of a reintervention (medical or surgical), costs, and chance of successful blood loss reduction may be added to the model and possibly gives new insights in the relative importance of each characteristic. In any case, a new patient preference study should also be conducted in a primary care population to gain a better understanding of the treatment preference of the overall group of women with HMB who consult their doctor for this complaint. A discrete choice experiment could be extended to include characteristics of other treatments in primary care, such as intermittent or daily medication intake. An alternative study design would be a qualitative research among patients (and GPs) to gain more in-depth insight in preferences and knowledge about the different treatment options for HMB.

HMB treatment

Oral medication

In this thesis we investigated the treatment of LNG-IUS and endometrial ablation for HMB. However, very few good quality comparative studies have been conducted on other drug treatment options. The Dutch College of GPs has prioritised research into the effectiveness of different treatments for HMB in both young women and perimenopausal women.[29] Women often have a preference for either hormonal or non-hormonal medical treatment. When a woman opts for oral hormonal medication, it is unclear whether the combined oral contraceptive pill is more effective than (long-cycle) progestogen therapy.[30,31] When a woman opts for non-hormonal treatment, there is low-quality evidence that tranexamic acid is superior to NSAIDs.[32] The results of a RCT comparing these treatment options can give an answer to this question. However, we think that more research needs

to be done into the women's and physicians' preferences and considerations that play a role in treatment choice before designing a RCT.

The LNG-IUS and/or endometrial ablation

We saw in our trial that 7% of the women in the LNG-IUS group and 10% of the women in the ablation group had a hysterectomy within 2 years of follow-up. The most common reasons for a reintervention were persistent HMB, dysmenorrhea and pelvic pain. At the moment, a RCT has started within the Dutch Gynaecology Consortium comparing endometrial ablation alone with endometrial ablation plus the LNG-IUS in women with HMB (MIRA 2 trial).[33] Adding a LNG-IUS to endometrial ablation inactivates the residual or regenerative endometrial tissue. The hypothesis is that this will reduce the pre-existing cyclical pelvic pain and iatrogenic pelvic pain induced by intrauterine adhesion formation associated with endometrial ablation. The women who are eligible for the MIRA 2 trial concern women who have completed their family and who are willing to receive both hormones (the LNG-IUS) and a more invasive, irreversible treatment (endometrial ablation).

In addition, we plan to compare the effect of the LNG-IUS strategy with the endometrial ablation strategy in the longer term (5 years follow-up of the MIRA trial). We would like to evaluate if there are additional interventions between 2 years and 5 years after randomisation and we would like to compare disease specific quality of life (MMAS) and menstrual blood loss (PBAC-score).

Who are the women in whom treatment fails?

We found that a subgroup of women, especially in the LNG-IUS group, had persistent HMB and a considerable proportion had the LNG-IUS removed and/or received a reintervention. Do these women differ from the women with successful treatment? We don't know yet. It is interesting to know if there are (baseline) characteristics that predict treatment failure. Among others, age, BMI, the severity of HMB and the presence of myomas have been studied as potential prognostic factors for treatment failure of the LNG-IUS. These results were conflicting. One study found that women with myomas of 2.5cm or larger had a higher risk of failure, whereas other studies found no difference in treatment effect in women with and women without myomas.[34-36] A lower BMI was found

to be a risk factor in one study.[37] Available evidence to date shows no influence of age on treatment effect.[36-38] The severity of HMB before treatment seems to be associated with treatment failure in two studies, but this could not be confirmed in another study.[36,38,39] Future research could focus on developing and validating a prognostic model. The results of this research can make it possible to counsel women on the expected benefits of treatment given her characteristics.

Integrating scientific research in general practice

We found in our qualitative study (Chapter 8) that participation in scientific research is not optimal integrated in daily general practice. Here is a discrepancy between goals stated on paper and daily practice. In their vision document 2022, the Dutch College of GPs and the Dutch National GP Association state that every general practice should participate structurally in education, research and innovation.[40] This contributes to the shared responsibility for the continuity and development of the discipline. Not every GP needs to be scientific researcher him/herself. But if participation in research becomes a rare task of GPs, this will endanger up-to-date knowledge in the future and leads to stagnation of primary care science. From the GPs' point of view, time constraints and prioritisation seemed to be important themes for the GPs participating in the MIRA trial. Although we did not extend our qualitative research with a quantitative questionnaire among a larger group of GPs to test this hypothesis, especially time constraints are often mentioned in other studies.[41,42] We would like to make some recommendations to tackle these barriers.

In the current era with increasing pressure on primary health care, it is important that invested time is also rewarded. This is one of the stumbling blocks as research funds are limited and it is often difficult to finance the researchers themselves. A minimal financial compensation equal to the GP rate, could flatten the threshold of investing time in research activities. If we want to maintain our high-quality GP care, both the government and the national GPs' organisations should give greater priority to integrate research into practice, both financially and logistically. Government subsidies are already available for the deployment of a practice manager. Subsidies could also be made available for the deployment of a research assistant who monitors and directs the current studies in a general practice. This policy is already widely used in hospitals. The MIRA trial was

conducted within the Gynaecology research consortium, allowing us to benefit from support from research nurses. Future expectations are that GP care will become more concentrated in larger health centres, making it more feasible to deploy a research assistant. Another option is to outsource these activities to a research assistant from the research department. Researchers will have to take into account more time and staff for patient recruitment when designing a study. This should therefore also be included in the financial budget for the grant provider. The importance of a collaboration between scientific research and clinical practice can be propagated more by the Dutch GP Association. For example by awarding accreditation points when participating in (a minimum number of) scientific studies.

A more difficult and more elusive theme is the attitude of GPs towards scientific research. This will also influence the prioritisation of research tasks. By integrating science more into the GP training programme, it may become more naturally to combine (participation in) scientific research and patient contact. This is in line with the Dutch attainment targets for GP training:

The GP should promote the development and implementation of professional knowledge by:

- collecting structured data for research and training;

- weighing new scientific insights on applicability in one's own practical situation.[43]

Further research is needed to investigate whether this actually leads to a different attitude among GPs (in training) and whether this leads to more satisfactory research participation.

Collaboration within General Practice

The MIRA trial was the first study performed within the Dutch Consortium of Benign Gynaecology in collaboration with the Dutch Consortium of General Practice. The Gynaecological consortium was founded in 2003 and has a trial agency that supports setting up and conducting multicentre research, and also plays a role in quality monitoring. The GP consortium exists since 2013, with the aim of creating optimal conditions for research in the field of primary medicine, including large-scale multicentre research. The national roll-out of the MIRA trial was seen as a pilot within the national GP consortium. Experiences from the MIRA trial help us to formulate recommendations

that can facilitate the conduction of multicentre research within the consortium: a clear protocol with whom to communicate from each institute and how to reach the GPs within each institute's network. What tasks should the researcher perform and what does the consortium facilitate? It must also be clear which research is eligible for conduction within the national consortium and how this selection is made. The National Research Agenda for General Practice Medicine, for example, provides guidance on important topics for future research.[29] The researcher could already indicate in the application how many institutes / regions (or how many general practices) should at least participate in order for the research to succeed.

Conclusions

A majority of women with HMB in primary care opt for a wait-and-see policy or treatment with oral medication. For women in whom this is not effective, the LNG-IUS and endometrial ablation are possible treatment options. Both strategies lead to a significant reduction in menstrual blood loss and comparable satisfaction and quality of life. There is a higher chance of needing additional interventions and it is taking longer to achieve the desired effect when starting with the LNG-IUS. These disadvantages must be weighed against a cheaper treatment strategy with the LNG-IUS, which can be easily started in primary care. Other characteristics such as a hormonal, contraceptive effect, invasiveness and reversibility, should be discussed with each individual woman before she can make a well-informed choice. Future research into treatment preferences and factors related to treatment success may contribute to this process of shared decision-making.

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