Systemic causes of heavy menstrual bleeding
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 9: Summary and general discussion
Summary

The thesis’ introduction first described haemostasis, during which we delved deeper into the roles of fibrinolysis and FXI on this mechanism. Next, the physiology of menstruation was described, including possible causes of heavy menstrual bleeding. This thesis addresses various underlying causes of heavy menstrual bleeding.

It is preferable if not every woman who presents with HMB, needs to be tested for underlying bleeding disorders. In chapter 2, we therefore validated the existing screening tool for bleeding disorders of Philipp et al. in a new cohort of women referred to the outpatient clinic of gynaecology with heavy menstrual bleeding (HMB). If this existing tool did not perform well, we wanted to develop a new clinical screening tool for bleeding disorders. We tested the screening tool in two hundred and five consecutive women with regular HMB (Pictorial Blood loss Assessment Chart-score of >100). In all patients gynaecological examination was performed, blood was drawn and a standardized questionnaire was filled out. The tool of Philipp was validated in our cohort. According to the bleeding disorder definition of Philipp, fifty-five patients (27%) in our cohort had a bleeding disorder of which 18/55 (33%) patients had a negative score on this screening tool, and 37/55 (67%) a positive score. This yielded a sensitivity of 67% and a specificity of 31% in our cohort, which is less sensitive than in the cohort of Philipp, and just slightly more specific. The positive likelihood ratio was 0.97 in our cohort, the negative likelihood ratio was 1.07.

If we used a more narrow definition of a bleeding disorder, defined as decreased fibrinogen (<1.0 g/dL), decreased von Willebrand factor (von Willebrand factor antigen (VWF:Ag) and/or von Willebrand ristocetin cofactor (VWF:RCO) < 50%), FVIII (<50%), FIX (<50%) and FXI (<65%), 11 women (5%) in our cohort had a bleeding disorder. When using the narrower definition, the sensitivity and specificity only improved slightly. Therefore we decided to develop a new screening tool. Covariates for the development of the new screening tool were selected by forward selection by univariate logistic regression. The 5 out of 16 variables we identified for our screening tool were: haemoglobin < 7.5 mmol/L (4 points), family member with a bleeding disorder (6 points), easy bruising (1 point), HMB since menarche (1 point) and bleeding after
procedure (2 points). With a cut-off of ≥1 point, sensitivity for no bleeding disorder was high (100%) with acceptable specificity (41%), reducing the proportion of women to be tested with 39%. Negative likelihood ratio was 0. Alternatively, the tool could be used to identify women with a high probability of a bleeding disorder by using a cut-off of ≥6 points (sensitivity: 27%, specificity: 96%, positive likelihood ratio: 6.75) (ROC-AUC: 0.76). We can conclude that we developed a simple screening tool, consisting of five variables, that reliably reduces the proportion of women with HMB that needed further testing for bleeding disorders with 39%. This tool needs to be validated in other groups of women with HMB.

In a previous study from our group we had the unexpected finding of a relatively low factor XI plasma level in women with heavy menstrual bleeding compared to healthy controls (FXI levels: 100 IU/dL vs 124 IU/dL, p<.001). In chapter 3 we wanted to confirm that FXI plasma levels in patients with heavy menstrual bleeding are lower than in controls. Furthermore, we wanted to investigate whether other coagulation parameters are also decreased in women with HMB without obvious deficiencies. One hundred and six patients with regular heavy menstrual bloodloss (Pictorial Blood loss Assessment Chart (PBAC)-score of >100) were included. In all patients gynaecological examination was performed, blood was drawn (blood count and haemostatic parameters) and a standardized questionnaire was filled out. Fifty three healthy controls were included, which had a regular cycle and subjectively normal blood loss. Patients (43 years (range 18-55)) were 10 years older on average than controls (33 years (range 20-51 years)) (p<.001). The median PBAC-score was higher in patients (307 points) than in controls (75 points) (p< .001). Twenty-eight percent of patients had a low haemoglobin (Hb<7.5 mmol/L) and 28% of the patients had gynaecological abnormalities. FXI levels were significantly lower in the patient group versus the control group (FXI 102 IU/dL vs 113 IU/dL; p=.002), even more pronounced when adjusted for age. No differences in FVIII, FIX, FXII and VWF:Ag were seen between patients and controls. In patients with and without gynecological abnormalities all measured coagulation parameters, including FXI levels, were not significantly different. In conclusion, we confirm that FXI levels in women with HMB are significantly lower compared to controls. The other coagulation parameters do
not show a similar pattern. Whether this relatively low FXI in patients plays a causative role or is the consequence of HMB is not clear.

Perhaps the relatively lower levels of FXI in patients can be explained by a differing distribution of SNP’s or mutations in F11 gene. The aim of the study in chapter 4 was to determine the single-nucleotide variants (SNVs) in the F11 gene in women with HMB. In addition we performed an extensive literature search to determine the clinical significance of each SNV. We included 49 patients referred for HMB. With direct sequencing analysis of all 15 exons and flanking introns of the F11 gene, we detected 29 different non-structural SNVs in women with HMB. Interestingly, most of these SNVs have previously been associated with venous thrombosis instead of bleeding. These findings have not helped to elucidate the molecular basis of HMB. They also question the specificity of previously reported F11 variations in patients with thrombosis. Additional studies are needed to explain the lower FXI levels seen in patients with HMB.

In chapter 5 the systemic fibrinolysis in women with heavy menstrual bleeding is tested. It is established that fibrinolysis in the endometrium plays a role in heavy menstrual bleeding. However, it was unknown whether increased systemic fibrinolysis might also increase the risk of heavy menstrual bleeding. Therefore we investigated fibrinolytic parameters, including clot lysis time (CLT), in women with heavy menstrual bleeding. We tested the fibrinolytic parameters in 79 patients with heavy menstrual bleeding (Pictorial Blood loss Assessment Chart score of > 100) and 28 controls (healthy volunteers without heavy menstrual bleeding). They underwent haemostatic testing in the first week after menstruation. The fibrinolytic parameters consisted of thrombin-activatable fibrinolysis inhibitor (TAFI) activity, and plasminogen activator inhibitor (PAI)-1, tissuetype plasminogen activator (tPA) and plasmin inhibitor (PI) levels and CLT. The systemic fibrinolytic parameters were similar between patients and controls, except for TAFI (89.4% vs. 82.5%) and PI (106% vs. 96%), the levels of which which were significantly higher in patients. In women with heavy menstrual bleeding without gynaecologic abnormalities, we found lower TAFI and PAI-1 levels than in women with gynaecologic abnormalities (TAFI, 85.4% vs. 94.8%; PAI-1, 16.0 g/L vs. 24.5 g/L). We can conclude that the systemic fibrinolytic capacity is not increased
in women with heavy menstrual bleeding. Overall, levels of the fibrinolytic inhibitors TAFI and PI were even higher in patients than in controls. However, in a subgroup of women without gynaecologic abnormalities, relatively lower levels of inhibitors may contribute to the heavy menstrual bleeding.

In clinical practice thyroid function is often tested in heavy menstrual bleeding (HMB), although strong evidence to support this procedure is lacking. The aim of the study in chapter 6 was to evaluate thyroid function in women with objectively diagnosed heavy menstrual bleeding. Two hundred and five consecutive patients were included in a study on systemic causes of HMB defined as Pictorial Blood loss Assessment Chart-score (PBAC) >100. Data were compared to female Nijmegen Biomedical Study population controls (n=1924). In patients in the first week after menstruation a gynaecological examination was performed and blood was taken. In 203 patients, TSH and FT$_4$ were measured. In patients the median PBAC-score was 285 (Q1-Q3:210-459), 33% of patients had anaemia (Hb<7.5 mmol/L). Overt hypothyroidism (TSH>4.0mU/L; FT$_4$<11.0pMol/L) was not seen in the patients, as opposed to 0.4% in the reference group (p=0.35). In the patients subclinical hypothyroidism (TSH>4.0mU/L; FT$_4$≥11.0pMol/L) was present in 5.4% versus 4.3% of controls (p=0.44). Overt (TSH<0.5mU/L; FT$_4$>19.5pMol/L) and subclinical (TSH<0.5mU/L; FT$_4$≤19.5pMol/L ) hyperthyroidism was found in 1.5% and 2.0% of the patients, vs 0.6% (p=0.16) and 0.8% (p=0.08) in controls, respectively. No significant differences in thyroid function were seen between patients with and without gynaecological abnormalities or those with and without coagulation disorders. We can conclude that thyroid dysfunction occurs in women with heavy menstrual bleeding, but not more often than in the general population. We conclude therefore that screening for thyroid dysfunction in women with HMB is not warranted.

In chapter 7 we describe a 70 year old Dutch woman with a FXI level of 30 %, consistent with a mild, heterozygous deficiency. She was diagnosed after bleeding following ophthalmic surgery and hip replacement. Total Tosetto bleeding score$^4$ was 10. Although it is generally believed that the haemostatic level of FXI is between 15-20%, correlation between the FXI level and the bleeding tendency is known to be weak.
and inconsistent. The molecular background of factor XI deficiency in this Dutch family (patient, two sisters, two daughters and one niece were tested) was determined. FXI levels were determined by a plasma clotting assay (Siemens). Direct sequencing analysis of all 15 exons and flanking introns of FXI gene was performed to detect causative mutations. The proband, her dizygotic twin sister (FXI 45%) and her niece (FXI 27%) were all affected with a novel heterozygous missense mutation resulting in a Threonine to Proline substitution at position 42 within exon 3. The other three family members were asymptomatic, had normal FXI levels and were not affected with a mutation in FXI gene. Multiple alignment analysis showed that Threonine is highly conserved among other species. A computer-based model (2f83) was used to evaluate the effect of the novel mutation on the molecular structure of FXI. Threonine 42 interacts with Phenylalanine 12, Serine 78, and Valine 59 through strong hydrogen bonds. After substitution, only an interaction remains with Valine 59. Furthermore, Proline could result in steric hindrance with Phenylalanine 41. We can conclude that we have identified a novel mutation that was associated with factor XI deficiency in a Dutch family.

In chapter 8 we have reviewed the gynaecological and obstetrical bleeding problems in women with a FXI deficiency. Menstrual bleeding, pregnancy and delivery present an intrinsic haemostatic challenge to women with bleeding disorders such as factor XI (FXI) deficiency. We give a systematic overview of studies on gynaecological and obstetrical bleeding problems in women with FXI deficiency. We searched MEDLINE, EMBASE and the Cochrane library for studies that present original data on the incidence of and treatment options for gynaecological and obstetrical bleeding in FXI-deficient women. We identified 27 studies, including a total of 372 women with FXI deficiency. All studies were observational, no interventional treatment studies were found. Most patients had a mild deficiency (FXI ≥ 20 IU d/L). Heavy menstrual bleeding (HMB) was reported in 7-67%. In 7/19 (37%) women who underwent gynaecological procedures, a bleeding complication occurred, including in 2/7 hysterectomies (29%). About 3-20% of reported pregnancies ended in a miscarriage; of these miscarriages 0-25% (4/23 miscarriages) were complicated by bleeding. Terminations of pregnancies
(TOP) were complicated by bleeding in 4 out of 11 cases (36%). In 90 out of 498 (18%) deliveries a postpartum haemorrhage (PPH) was reported, ranging from 0 to 50% in individual studies. In 21% (66/321) of deliveries, prophylaxis was given. This was associated with 9% (6/66) PPH, compared to 19% in deliveries without prophylaxis (84/432). Epidural analgesia was performed without complications in 44 patients.

Women with FXI deficiency have a clearly increased risk of HMB, and of bleeding complications after miscarriage, TOP and delivery. No high quality data are available regarding prophylactic treatment.

**General discussion and future perspectives**

Heavy menstrual bleeding negatively affects the lives of one fifth of women in the reproductive age. This thesis addresses various underlying causes of heavy menstrual bleeding.

All our studies have been conducted in the patient population referred to the menstruation outpatient clinic of the UMCG for heavy menstrual bleeding.

Women were all in the premenopausal phase, but the average age of the patients was above 40 years. Common reasons for consultation were ‘being done with so many years of heavy menstrual bleeding’ and no child wish any more. These presenting reasons could be an explanation for the higher age, found in our studies if compared with other studies. In the study of Shapley et al. another common reason for consultation was interference with life because their ‘mood’ was influenced.

Our patients had high PBAC scores (307 points, range 105-1063), if compared with other studies. Surprisingly, also 30% of the Dutch controls had high PBAC scores of ≥100 points. Based on a PBAC score with a cutoff value of 100 points alone, women can not be diagnosed with heavy menstrual bleeding. The controls did not experience their amount of blood loss as a problem. The World Health Organization takes account of the subjective experience of heavy menstrual bleeding, as defined by: ‘For clinical purposes, heavy menstrual bleeding should be defined as excessive menstrual blood loss, which interferes with the woman’s physical, emotional, social and material quality of life, and which can occur alone or in combination with other symptoms.’
Despite the fact that the diagnosis of heavy menstrual bleeding is essentially subjective, it is often useful to have an additional objective measurement, such as the PBAC score. An issue with this is the cutoff that should be used. In the present time, with adequate nutritional status of women in the Western world, the body often has enough (iron) reserves for a considerable amount of blood loss every month. Therefore in our population, women will not seek medical attention for heavy menstrual bleeding if it is not interfering with their daily activity. This illustrates that a PBAC-score of ≥100 might be very sensitive, but the score is not specific in the Western European setting. Other studies confirm that a PBAC score of ≥150 is a more accurate cut-off level in clinical practice. However, in our study, we preferred to use the ≥100 points international cut-off value of the PBAC score to make the comparison with other cohorts possible.

During the consultations, it was evident that patients were usually not interested in the cause, but would just like treatment for their heavy menstrual bleeding. Still, we were glad that all these women agreed to collaborate in our research. Also, the responses of controls revealed that women find this an important issue, especially to help others. Most patients received treatment, like antifibrinolytics, nonsteroidal anti-inflammatory drugs, the contraceptive pill, intrauterine device, progestogens, endometrial ablation or hysterectomy. Although oral contraceptives are advised as the treatment of first choice, 77% of women are not satisfied after this therapy. In our cohort, most of the patients had already tried the pill and preferred a different kind of treatment such as an LNG-IUD or endometrial destruction. A Cochrane review showed that Levonorgestrel-releasing intrauterine device (LNG-IUD) is more effective than cyclic norethisterone (for 21 days), however, some women with LNG-IUD experience side effects such as pelvic pain and breast tenderness. Endometrial destruction techniques, which aim to destroy or remove the endometrial tissue, have become alternatives to hysterectomies for menorrhagia, and as a result, the number of hysterectomies has declined impressively. The effectiveness of endometrial ablation has been evaluated by several RCTs showing a satisfaction rate of about 90%. In our studies we focussed on the systemic factors that may underlie the heavy menstrual bleeding.
There is evidence that fibrinolysis in the endometrium plays an important role in menstruation. In women with heavy menstrual bleeding increased fibrinolytic activity was observed in the menstrual fluid, which suggested that this might be a contributing factor in the aetiology of heavy menstrual bleeding\textsuperscript{19,20}. In this thesis, we describe the first study of systemic fibrinolysis that has been performed in this setting. Remarkably, in our study, we found no increased systemic fibrinolysis and inhibitors of fibrinolysis (thrombin activatable fibrinolysis inhibitor (TAFI) and plasmin inhibitor (PI)) were even higher in patients with heavy menstrual bleeding. An explanation for this could be the moment of testing in the menstrual cycle. We measured the fibrinolytic parameters one week after the menstruation. This is the week in which the body has used many of its reserves to compensate for the blood loss during the menstruation. Because of that, we may only see the increased production of fibrinolytic parameters and not the continuous low levels during the menstrual cycle. We hypothesize that there is cyclic variation in menstruating women. Therefore a (pilot) study where the cyclic variation in fibrinolytic parameters in women with heavy menstrual bleeding and in women with normal menstrual blood loss is measured four times in one menstruation cycle is under way.

In a previous study concerning underlying bleeding disorders, we had the unexpected finding that patients had significantly longer aPTT compared to controls (26.5 vs 25.0 sec; \(p=0.001\)), explained by relatively lower levels of FXI (100 vs 124 IU/dL; \(p<.001\)) in patients\textsuperscript{3}. In our confirmation study, the FXI levels in women with heavy menstrual bleeding were again significantly lower compared with controls (FXI 102 IU/dL vs 113 IU/dL; \(p=.002\)). In a previous study by Kadir et al.\textsuperscript{21} FXI levels showed no cyclic relationship over the monthly period in women with a regular cycle and no heavy menstrual bleeding. In this study they did not make the comparison of patients with cycle-controlled control subjects. Other studies\textsuperscript{22-26} were not designed to find lower but not deficient levels of factor XI. Whether this relatively low FXI in patients is underlying or is the consequence of heavy menstrual bleeding is not clear. One would need to investigate the cyclic variation in FXI levels in women with HMB in comparison to cycle-controlled controls. The difference in FXI levels will not result in changes in the treatment of women with HMB. In addition, there is no explanation
for the relatively low FXI levels or bleeding tendency in women with heavy menstrual bleeding by measuring mutations and SNPs in the F11 gene. Perhaps there is a relationship between the cyclic variation in systemic fibrinolysis and FXI levels in women with HMB, which can result in a better understanding of the effectiveness of tranexamic acid in certain patients.

International guidelines advise to measure the thyroid function in women with heavy menstrual bleeding. Thyroid dysfunction occurs in women with heavy menstrual bleeding, but not more often than in the general population. In the Dutch Guideline for Heavy Menstrual Bleeding the advice is already not to screen for thyroid dysfunction, but this advice is based on small sample sized studies. In our study we confirm the statement that thyroid function should not be screened for in women with HMB.

In our systematic review, we have shown that women with a factor XI deficiency have a clearly increased risk of HMB, but also of bleeding complications after miscarriage, terminations of pregnancy and delivery. Currently, available therapy for FXI deficiency consists of antifibrinolytic agents and FXI replacement either with FXI concentrate or with fresh frozen plasma. Both of these FXI replacement therapies are blood products and are associated with side-effects including a potential risk of transmissible infections. There are no high quality studies that could guide decisions to give or withhold prophylaxis in women with FXI deficiency. Therefore, future studies should ideally include consecutive cohorts of patients, be large enough (ie multicentre) and follow the appropriate international standards for the definitions of factor XI deficient patients (severe vs non-severe, bleeder vs non-bleeder) and other aspects (heavy menstrual bleeding, post-partum haemorrhage etc.). Ideally experimental studies must be conducted for the prophylactic treatment in (elective) surgeries for better evidence based guidelines.

The screening tool we developed is a non-invasive accessible way to screen women with heavy menstrual bleeding and a potential bleeding disorder. The tool could lead to a 39% decrease of additional testing if all women who present with HMB were tested. Screening women when they first present with HMB, bleeding disorders can be diagnosed in an early stage, leading to both cost savings and fewer
bleeding complications. Our screening tool has not been validated beyond the initial study population. Additional testing to validate the tool must be undertaken in further research to draw a firm conclusion whether this is a reliable screening tool.

Heavy menstrual bleeding is a multi-causal problem, of which coagulation can be an important component. (Systemic) fibrinolysis is a subarea which deserves further research. In addition, strategies to screen for underlying clotting disorders to the attention should receive higher priority.
References
