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Effect of lower VWF and FXI levels on
levonorgestrel intrauterine system and
endometrial ablation treatment success
in heavy menstrual bleeding –
an explorative study

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ABSTRACT

Background

There is an increased prevalence of coagulation factor deficiencies among women with heavy menstrual bleeding (HMB). Whether coagulation factors levels influence treatment success for HMB is unknown.

Objectives

To explore the prevalence of decreased levels of Factor XI (FXI) and von Willebrand Factor (VWF) in women with HMB and to investigate if coagulation factor levels are associated with the effectiveness (Pictorial Blood Assessment Chart-score ≤ 75 points and no surgical reintervention) of the levonorgestrel intrauterine system (LNG-IUS) and endometrial ablation.

Methods

An explorative observational study alongside a multicentre RCT, comparing LNG-IUS and endometrial ablation in women with HMB. We performed logistic regression analyses to investigate the association between FXI and VWF levels and treatment effect.

Results

Ninety-five women participated, 93 could be analysed. Median FXI was 122.4% (below the lower limit of normal (LLN) in 1 woman), median VWF was 90% (below LLN in 3 women). In the endometrial ablation group (but not in the LNG-IUS group), women with FXI below the median had a lower chance of effective treatment compared to women with FXI above the median (OR 0.08, 95% CI 0.01 – 0.68). In both treatment groups, no differences in treatment success were seen between higher and lower VWF antigen levels.

Conclusions

This explorative study indicates that in women with lower FXI activity, endometrial ablation might be less effective than in women with higher FXI activity. Further research is needed before recommendations for optimal HMB treatment in women with low coagulation factors can be given.

INTRODUCTION

Heavy menstrual bleeding (HMB) is the most prevalent symptom in women with bleeding disorders and has a major impact on their quality of life. In the Dutch WiN study, a nationwide sample of patients with moderate or severe von Willebrand disease (VWD), 81% of women reported HMB. In those over 40 years of age, 28% had had a hysterectomy.¹ The Low von Willebrand in Ireland Cohort study included patients with milder VWD, but also reported 89% HMB in the female participants.² A systematic review of cohort studies including women with mostly mild factor XI (FXI) deficiency reported an estimated prevalence of HMB of 21%.³ Similar data have been reported in carriers of haemophilia.⁴

A large proportion of women with HMB has an underlying bleeding disorder: a meta-analysis of 11 studies concluded that 13% of these women have VWD.⁵ Mild FXI deficiency is also relatively prevalent at around 4%.^{6,7} Other coagulation factor deficiencies are more rare in women with HMB. The frequency of platelet disorders might be even higher than that of VWD and FXI deficiency, but studies on these disorders are subject to a large variation in diagnostic criteria.⁸ Another aspect is that, in women with HMB without evident coagulation factor deficiencies, lower levels of von Willebrand factor (VWF) and FXI are found compared to controls without HMB.⁷ Data on the treatment of HMB in women with bleeding disorders or low levels of coagulation factors is scarce.⁹ Specific treatment, with for instance desmopressin (DDAVP) or factor concentrates, can be prescribed but this is often inconvenient and expensive. In most cases, the same treatment modalities as in the general population are used.^{10,11} The relative effectiveness of these treatment modalities has not been studied in women with bleeding disorders. This might not be an issue for easy to use, affordable, safe and reversible options such as combined oral contraceptives or tranexamic acid. However, it is relevant when women have to choose between more invasive, longer acting or even irreversible treatments.

The recently completed MIRA trial compared two treatment strategies for HMB, randomising women without diagnosed bleeding disorders between the levonorgestrel intrauterine system (LNG-IUS) and endometrial ablation.^{12,13} In the study that we report here, we explored the prevalence of decreased levels of FXI and VWF in women with HMB

and investigated if levels of these coagulation factors are associated with the effectiveness of the LNG-IUS and endometrial ablation in women with HMB.

METHODS

Study design

An explorative observational study was conducted alongside a multicentre randomised controlled trial (MIRA trial). This trial was performed by the Dutch Consortium for Studies in Women's Health and the department of General Practice of the University Medical Centre Groningen and was conducted in 26 general and university hospitals and 197 nearby general practices in the Netherlands. After giving written informed consent women were randomised to a strategy starting with the LNG-IUS or a strategy starting with endometrial ablation. In study centres where the local laboratory was willing to participate in the MIRA trial (n=11 laboratories), women were asked separate informed consent for taking and analysing blood on coagulation FXI activity and VWF antigen (VWF:Ag) levels. The study was conducted according to the principles of the Declaration of Helsinki and has been approved by the ethics committee of the Academic Medical Centre Amsterdam, the Netherlands (registration number 2011_372).

Study population

Women aged 34 years or older suffering from HMB, with a Pictorial Blood Assessment Chart (PBAC) score exceeding 150 points, were eligible to participate in the MIRA trial. The PBAC is a validated method for assessment of menstrual blood loss by multiplying the number of lightly, moderately and heavily soiled tampons and pads by fixed factors.¹⁴ Women were excluded if they had a future pregnancy wish, abnormal cervix cytology in the past 5 years, uterus length of more than 10cm, intracavitary fibroids or polyps or large intramural fibroids determined by either a transvaginal ultrasound or bimanual vaginal examination. Further details about the study design and study population of the MIRA trial are published elsewhere.¹²

Outcome measures

Prevalence of decreased FXI activity and VWF:Ag levels

A lower limit of normal (LLN) of 65% for FXI activity and 50% for VWF:Ag was used to define decreased levels of FXI and VWF, according to local laboratory reference values.

Association of FXI activity and VWF:Ag levels with the effectiveness of LNG-IUS and endometrial ablation treatment

Our primary outcome for effectiveness in the LNG-IUS and endometrial ablation group was the proportion of women with a PBAC-score ≤ 75 points at 24 months of follow-up.¹⁵ Women were allowed to undergo a reintervention during the follow-up period of the MIRA trial. Therefore, we performed a second analysis with a composite outcome: the proportion of women with a combination of (1) a PBAC-score ≤ 75 points and (2) no surgical reintervention (endometrial ablation or hysterectomy) at 24 months follow-up.

Laboratory methods

At baseline, 12 ml citrated blood was taken from participants of the MIRA trial who gave additional informed consent for blood assessment. The blood was centrifuged and plasma was stored at -80°C until the end of the follow-up period. Laboratory measurements of FXI level activity and VWF:Ag were performed after 24 months of follow-up. VWF:Ag was measured using Enzyme-Linked Immuno Sorbent Assay (ELISA) with polyclonal rabbit anti-human VWF antiserum (Dako, Glostrup, Denmark). FXI activity was determined by a one-stage clotting assay with APTT reagents, Standard Human Plasma and factor deficient plasma on a CS2100i coagulation analyser, all from Siemens (Marburg, Germany). The technician performing the laboratory analysis was blinded for treatment allocation and treatment effect.

Statistical analysis

Descriptive statistics are presented both for the total study population, the LNG-IUS group and the endometrial ablation group. Continuous data are presented in means and standard deviations (SD) or median and interquartile range (IQR) as appropriate and dichotomous or nominal data in numbers and percentages. A formal sample size calculation was not performed, since the number of participants in this explorative study

was determined by the number of women that were recruited in the MIRA trial (n=270) and gave additional informed consent for blood assessment.

We performed univariate logistic regression analyses to investigate if FXI activity and VWF:Ag levels were associated with the effectiveness of the LNG-IUS and endometrial ablation. The proportion of women with a PBAC-score ≤ 75 points (analysis I) or the proportion of women with a PBAC-score ≤ 75 points without a surgical reintervention (analysis II) were included in the model as the dependent variable. Treatment (LNG-IUS or endometrial ablation) and FXI activity or VWF:Ag levels (categorical variables: below and above the median) were included in the model as independent variables. We performed logistic regression analyses for both coagulation factors combined (categorical variables: zero, one or two factors above the median) as well as for FXI activity and VWF:Ag separately. Odds ratios (OR) with 95% confidence intervals were calculated. Statistical analyses were performed using the software Statistical Package for the Social Sciences, version 23 (SPSS, Inc., Chicago, IL, USA).

RESULTS

We received blood samples from 95 participants of the MIRA trial (n=43 in the LNG-IUS group and n=52 in the endometrial ablation group). Baseline characteristics are presented in Table 1. Ninety-three patients were included in the logistic regression analysis, 2 excluded patients had missing data on the primary outcome of effectiveness (PBAC-score).

Table 1. Baseline characteristics

	Endometrial Ablation (n=52)	LNG-IUS (n=43)	Total study population (n=95)
Age	45.3 (±5.2)	45.6 (±4.7)	45.4 (±5.0)
BMI*	28.6 (±5.7)	28.1 (±5.6)	28.4 (±5.6)
Duration of menstruation (days)	8 (5 – 10)	7 (7 – 10)	7 (6 – 10)
Baseline PBAC-score	644.6 (±521.7)	639.6 (±532.4)	642.3 (±523.6)
Previous uterus surgery			
Myomectomy	7 (13.5%)	3 (7.0%)	10 (10.5%)
Polypectomy	1 (1.9%)	2 (4.7%)	3 (3.2%)
Anti-coagulants use			
Platelet aggregation inhibitors	0 (0%)	1 (2.3%)	1 (1.1%)
Vitamin K antagonists	1 (1.9%)	0 (0%)	1 (1.1%)
Hormonal medication use†	4 (7.7%)	6 (14.0%)	10 (10.5%)
Haemoglobin‡ (mmol/L)	7.5 (±1.0)	7.7 (±1.0)	7.6 (±1.0)

LNG-IUS: levonorgestrel intrauterine system. BMI: Body Mass Index. PBAC: Pictorial Blood Assessment Chart. Values are given as means (± standard deviation), median (IQR) or number (%).

* N= 6 missing in the endometrial ablation group; N= 8 missing in the LNG-IUS group. † Including estrogen use. ‡ N= 22 missing in the endometrial ablation group; N= 22 missing in the LNG-IUS group.

Prevalence of decreased FXI activity and VWF:Ag levels

The prevalence of decreased FXI activity levels (<65%) in our study population was 1.1% (one woman in the endometrial ablation group). The prevalence of decreased VWF:Ag levels (<50%) was 3.2%; one woman in the endometrial ablation group and two women in the LNG-IUS group (Table 2). None of the women had both FXI activity and VWF:Ag levels below the LLN. The median FXI level activity in our study population was well above 100% (122.4%), whereas the median VWF:Ag level was below 100% (90%).

Table 2. FXI activity and VWF:Ag levels

	Endometrial Ablation (n=52)	LNG-IUS (n=43)	Total study population (n=95)
Factor XI (median; IQR)	120.7% (95.7-139.1)	123.5% (97.2-137.0)	122.4% (96.6-137.0)
Factor XI < LLN (<65%)	1 (1.9%)	0 (0%)	1 (1.1%)
VWF:Ag (median; IQR)	87.5% (69.3-111.8)	93.0% (76.0-120.0)	90.0% (70.0-112.0)
VWF:Ag < LLN (<50%)	1 (1.9%)	2 (4.7%)	3 (3.2%)

LNG-IUS: levonorgestrel intrauterine system. LLN: Lower Limit of Normal. VWF:Ag: von Willebrand Factor Antigen. Values are given as number (%), unless otherwise indicated.

Analysis I: Association of FXI activity and VWF:Ag levels with the effectiveness of LNG-IUS and endometrial ablation treatment (PBAC ≤75)

There was a non-significant trend in the endometrial ablation group towards lower success rates (PBAC ≤75) when coagulation levels were lower. This trend was not seen in the LNG-IUS group (Table 3).

Table 3. Coagulation factor levels (combined) and effectiveness of treatment (PBAC ≤75) (n=93)

	Endometrial Ablation (n=51)		LNG-IUS (n=42)	
	PBAC ≤ 75		PBAC ≤ 75	
	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Factor XI and VWF:Ag ≥ median	15/16 (93.8%)	1	12/14 (85.7%)	1
Factor XI or VWF:Ag ≥ median	16/18 (88.9%)	0.53 (0.04–6.51)	15/17 (88.2%)	1.25 (0.15–10.2)
Factor XI and VWF:Ag < median	14/17 (82.4%)	0.31 (0.29–3.35)	9/11 (81.8%)	0.75 (0.09–6.4)

LNG-IUS: levonorgestrel intrauterine system. PBAC: Pictorial Blood Assessment Chart. VWF:Ag: Von Willebrand Factor Antigen. Values are given as number (%) or odds ratios with 95% confidence intervals. Coagulation factor levels ≥ the median are used as the reference group.

Additionally, analyses were performed separately for lower FXI activity and VWF:Ag. All four women with a coagulation factor level below the LLN were successfully treated

(PBAC ≤ 75) with either the LNG-IUS or endometrial ablation. In the endometrial ablation group, women with FXI activity below the median seemed to have a lower chance of effective treatment compared to women with FXI activity above the median (81% versus 96%). However, this association was not statistically significant (OR 0.18, 95% CI 0.02-1.62). In the LNG-IUS group, success rates were comparable in the women with FXI activity below and above the median. The success rates between women with VWF:Ag levels above and below the median did not seem to differ in both treatment groups (Table 4).

Table 4. Factor XI and VWF:Ag levels and effectiveness of treatment (PBAC ≤ 75) (n=93)

	Endometrial Ablation (n=51)		LNG-IUS (n=42)	
	PBAC ≤ 75		PBAC ≤ 75	
	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Factor XI \geq median	24/25 (96.0%)	1	19/22 (86.4%)	1
Factor XI < median	21/26 (80.8%)	0.18 (0.02-1.62)	17/20 (85.0%)	0.90 (0.16-5.04)
Factor XI < LLN	1/1 (100%)		0/0	
VWF:Ag \geq median	22/25 (88.0%)	1	20/23 (87.0%)	1
VWF:Ag < median	23/26 (88.5%)	1.05 (0.19-5.74)	16/19 (84.2%)	0.80 (0.14-4.51)
VWF:Ag < LLN	1/1 (100%)		2/2 (100%)	

LNG-IUS: levonorgestrel intrauterine system. PBAC: Pictorial Blood Assessment Chart. LLN: Lower Limit of Normal. VWF:Ag: Von Willebrand Factor Antigen. Values are given as number (%) or odds ratios with 95% confidence intervals. Coagulation factor levels \geq the median are used as the reference group.

Analysis II: Association of FXI activity and VWF:Ag levels with the effectiveness of LNG-IUS and endometrial ablation treatment (PBAC ≤ 75 without surgical reintervention)

Analysis II (a PBAC-score ≤ 75 without reintervention as an outcome measure for treatment success) showed a non-significant trend that was comparable to analysis I when FXI activity and VWF:Ag levels were combined. In the endometrial ablation group, women with lower coagulation factor levels seemed to have a lower chance of treatment success compared to women with higher coagulation factor levels (Table 5). This trend was not seen in the LNG-IUS group.

Table 5. Coagulation factor levels (combined) and effectiveness of treatment (PBAC ≤ 75 without surgical reintervention) (n=93)

	Endometrial Ablation (n=51)		LNG-IUS (n=42)	
	PBAC ≤ 75 and no reintervention		PBAC ≤ 75 and no reintervention	
	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Factor XI and VWF:Ag \geq median	15/16 (93.8%)	1	8/14 (57.1%)	1
Factor XI or VWF:Ag \geq median	14/18 (77.8%)	0.23 (0.02–2.35)	12/17 (70.6%)	1.80 (0.41–7.96)
Factor XI and VWF:Ag $<$ median	12/17 (70.6%)	0.16 (0.02–1.56)	7/11 (63.6%)	1.31 (0.26–6.64)

LNG-IUS: levonorgestrel intrauterine system. PBAC: Pictorial Blood Assessment Chart. VWF:Ag: Von Willebrand Factor Antigen. Values are given as number (%) or odds ratios with 95% confidence intervals. Coagulation factor levels \geq the median are used as the reference group.

In table 6, the separate analyses for FXI activity and VWF:Ag are presented.

Table 6. Factor XI and VWF:Ag levels and effectiveness of treatment (PBAC ≤ 75 without surgical reintervention) (n=93)

	Endometrial Ablation (n=51)		LNG-IUS (n=42)	
	PBAC ≤ 75 and no reintervention		PBAC ≤ 75 and no reintervention	
	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Factor XI \geq median	24/25 (96.0%)	1	14/22 (63.6%)	1
Factor XI $<$ median	17/26 (65.4%)	0.08 (0.01–0.68)	13/20 (65.0%)	1.06 (0.30–3.76)
Factor XI $<$ LLN	1/1 (100%)		0/0	
VWF:Ag \geq median	20/25 (80.0%)	1	14/23 (60.9%)	1
VWF:Ag $<$ median	21/26 (80.8%)	1.05 (0.26–4.19)	13/19 (68.4%)	1.39 (0.39–5.01)
VWF:Ag $<$ LLN	1/1 (100%)		2/2 (100%)	

LNG-IUS: levonorgestrel intrauterine system. PBAC: Pictorial Blood Assessment Chart. LLN: Lower Limit of Normal. VWF:Ag: Von Willebrand Factor Antigen. Values are given as number (%) or odds ratios with 95% confidence intervals. Coagulation factor levels \geq the median are used as the reference group.

In the endometrial ablation group, the women with FXI activity below the median had a lower chance of effective treatment compared to the women with FXI activity above the median (65.4% versus 96.0%; OR 0.08, 95% CI 0.01 – 0.68; Table 6). There was no difference in treatment success of endometrial ablation in women with VWF:Ag below the median compared to women with VWF:Ag above the median. In the LNG-IUS group, no differences between women with lower and higher FXI activity and VWF:Ag levels were seen (Table 6).

DISCUSSION

In this explorative study in women with HMB, the prevalence of FXI activity and VWF:Ag levels below the LLN were 1.1% and 3.2%, respectively. We found that lower FXI activity levels may be associated with a lower chance of treatment success of endometrial ablation compared to higher FXI activity levels. This association was only significant for the composite outcome of treatment success: a PBAC-score ≤ 75 without reintervention, not for treatment success defined as a PBAC-score ≤ 75 . Lower levels of VWF did not seem to influence the treatment effect of endometrial ablation or the LNG-IUS. A possible explanation for our findings may be that lower levels of FXI activity predispose for bleeding in places with a high fibrinolytic activity.¹⁶ This has been shown for deficient levels, but might also be the case for variation within the normal range: in a previous study, we showed that women with HMB had on average lower levels of FXI than controls.⁷ Increased fibrinolytic activity in the endometrium could play a role.¹⁷ However, it is unclear how this would differentially impact the effectiveness of endometrial ablation. Previous research into the association between decreased coagulation levels and the treatment effect of the LNG-IUS or endometrial ablation is limited to small cohorts describing the effect of a single intervention in women with diagnosed coagulation disorders.^{18,19} El Nashar et al. found comparable results regarding treatment failure, quality of life and patient satisfaction after endometrial ablation in women with and without bleeding disorders (VWD, thrombocytopenia and women with warfarin use).^{20,21} Ours is the first study exploring the relation between actual coagulation levels and effect of HMB treatment.

The prevalence numbers of decreased coagulation levels in our study are remarkably lower than the prevalence found in earlier studies in women with HMB (4% for decreased FXI and 13% for VWD).⁵⁻⁷ The probable explanation for this is that we included patients from primary and routine gynaecological care who had no wish to preserve fertility. Women with coagulation disorders are more likely to present with HMB at a younger age and the prevalence will be higher in specialist centres.²² As we saw in our previous study, the median level of VW:Ag was relatively low in this study. Conversely, the median of level of factor XI was relatively high. This observation is hard to interpret in the absence of a matched control population: we previously showed that for factor XI, levels in healthy age and sex- matched controls can differ significantly from the mean of the laboratory normal range.⁷

Since we recruited women in routine practice, including general practice, our study population is possibly more generalizable to the general population and adds to the estimation of the prevalence range of decreased coagulation factor levels in women with HMB. Our assessment of decreased coagulation factors is based on a single measurement. We choose to measure VWF:Ag instead of activity, in line with previous studies. This could have led to missing cases of mild type 2 VWD variants. Another limitation is that 10% of women in our study used hormonal medication with estrogens at baseline. Estrogens can raise VWF blood levels.^{23,24} This may have led to an underestimation of the prevalence of decreased VWF:Ag levels. Besides generalizability of the study population, a strength of our study was that analysis of coagulation factor levels was performed after the data collection on the primary outcome, which reduces the risk of bias.

Although nearly 100 women participated in our study, the sample size was too small to draw firm conclusions and our findings can only be seen as explorative. We chose to divide coagulation levels in categories below and above the median in the logistic regression analysis, because we hypothesized an effect of coagulation factors over their full range. Also, the number of patients with coagulation levels below the LLN (actual number: 0 to 2 per treatment group) would be too small to perform statistical analyses. We assume that the finding that all patients with FXI activity or VWF:Ag below the LLN had a 100% treatment success, is a coincidence rather than a real association with an underlying physiological explanation. The present study was not designed nor large

enough to compare LNG-IUS and endometrial ablation in strata of coagulation factor levels. Comparing the two treatment strategies in a noninferiority design was the aim of the main study, results of which have been reported separately.¹³ In short, the proportion of women successfully treated (PBAC-score ≤ 75) was not significantly different between the two treatment strategies. When we take in account the chance of a reintervention, the LNG-IUS appears less effective. This outcome is to be expected as the LNG-IUS is a less invasive treatment with more possibilities with regard to (surgical) reinterventions. Further research is needed to explore the possible relation between lower FXI level activity and decreased treatment effect of endometrial ablation and the underlying mechanism. Acknowledging the limitations that this study has in comparing the two treatment strategies, we have no indication that endometrial ablation is inferior compared to LNG-IUS in the treatment of HMB in women with lower FXI activity levels. Until more knowledge is gathered, current treatment recommendations for HMB in women with decreased coagulation factor levels should be in line with guideline recommendations for women without coagulation disorders.

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