Effect of lower VWF and FXI levels on levonorgestrel IUS and endometrial ablation treatment success in heavy menstrual bleeding

van den Brink, Marian J; Wiewel-Verschueren, Sophie; Beelen, Pleun; van Borselen, Joep W; Bongers, Marlies Y; Lukens, Michaël V; Dekker, Janny H; Meijer, Karina

Published in:
Haemophilia

DOI:
10.1111/hae.14392

Received: 5 March 2021 | Revised: 13 July 2021 | Accepted: 25 July 2021

DOI: 10.1111/hae.14392

Haemophilia WILEY

LETTER TO THE EDITOR

Effect of lower VWF and FXI levels on levonorgestrel IUS and endometrial ablation treatment success in heavy menstrual bleeding: An exploratory study

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] In Dutch women with rare bleeding disorders, 77% reported HMB. In—mostly mild—factor XI deficiency, this proportion was 55%.[2] Similar data have been reported in carriers of haemophilia.[3]

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.[4] Mild FXI deficiency is also relatively prevalent at around 4%.[5] Other coagulation factor deficiencies are rare in women with HMB. Another aspect is that, in women with HMB without evident coagulation factor deficiencies, lower levels—although still in de normal range—of von Willebrand factor (VWF) and FXI are found compared to controls without HMB.[5]

Data on the treatment of HMB in women with bleeding disorders or low levels of coagulation factors is scarce.[6] 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.[7] The relative effectiveness of these treatment modalities has not been studied in women with bleeding disorders. 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.[8] In an exploratory observational study conducted alongside the MIRA trial, 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.

The MIRA trial randomised women aged 34 years or older suffering from HMB, with a Pictorial Blood Assessment Chart (PBAC)[9] score exceeding 150 points at study entry, to a strategy starting with the LNG-IUS or with endometrial ablation. Women were allowed to undergo a re-intervention during the follow-up period of the MIRA-trial. In 11 study centres with a participating local laboratory, women were asked additional informed consent for the present study. The study was approved by the ethics committee of the Amsterdam University Medical Centre, the Netherlands (registration number 2011_372).

Outcome measures were prevalence of decreased FXI activity (<65%) and VWF:Ag levels (<50%), both according to local laboratory reference values, and effectiveness of LNG-IUS and endometrial ablation treatment. Effectiveness was defined as a composite outcome: the proportion of women with a PBAC score ≤ 75 points without a surgical re-intervention (endometrial ablation or hysterectomy) at 24 months follow-up. A PBAC score ≤ 75 points is considered controlled bleeding.[10]

Citrated blood samples were taken at baseline, taking care to avoid close relation to procedures, to prevent acute phase reactions. Plasma was stored at -80°C, until measurements 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).

A formal sample size calculation was not performed, since the number of participants in this exploratory study was determined by the number of women that were recruited in the MIRA trial ($n = 270$) and gave additional informed consent for coagulation factor assessment.

We performed univariate logistic regression analyses to investigate if FXI activity and VWF:Ag levels (categorical variables: below and above the median) were associated with the effectiveness of the LNG-IUS and endometrial ablation. 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).

Of the 270 MIRA participants, 229 were from centres with participating laboratories, and 124 consented to this sub-study. Of these, 29 did not have blood drawn or withdrew consent. We included 95 participants, baseline characteristics are presented in Table 1. Two had missing data on the effectiveness outcome (PBAC-score).

One woman (1.1%) had a decreased FXI activity level (61%). Three women (3.2%) had decreased VWF:Ag levels (42, 44 and 49%, respectively). The median FXI level activity in our study population was well

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[ba]	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%)
Estrogen 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)

Values are given as means (± standard deviation), median (IQR) or number (%).
Abbreviations: LNG-IUS: levonorgestrel intrauterine system. BMI: Body Mass Index. PBAC: Pictorial Blood Assessment Chart.
[ba]N = 6 missing in the endometrial ablation group; *N* = 8 missing in the LNG-IUS group.
[‡]N = 22 missing in the endometrial ablation group; *N* = 22 missing in the LNG-IUS group.

TABLE 2 Factor XI and VWF:Ag levels and effectiveness of treatment (PBAC ≤75 without surgical re-intervention) ($n = 93$)

	Endometrial ablation ($n = 51$) PBAC ≤ 75 without a re-intervention		LNG-IUS ($n = 42$) PBAC ≤ 75 without a re-intervention	
	N (%)	OR (95% CI)	*N* (%)	OR (95% CI)
Factor XI and VWF:Ag ≥ median	15/16 (93.8%)	1	8/14 (57.1%)	1
Factor XI or VWF:Ag ≥ median	14/18 (77.8%)	.23 (.02 – 2.35)	12/17 (70.6%)	1.80 (.41 – 7.96)
Factor XI and VWF:Ag < median	12/17 (70.6%)	.16 (.02 – 1.56)	7/11 (63.6%)	1.31 (.26 – 6.64)
Factor XI ≥ median	24/25 (96.0%)	1	14/22 (63.6%)	1
Factor XI < median	17/26 (65.4%)	.08 (.01 – .68)	13/20 (65.0%)	1.06 (.30 – 3.76)
Factor XI < LLN	*1/1 (100%)*		*0/0*	
VWF:Ag ≥ median	20/25 (80.0%)	1	14/23 (60.9%)	1
VWF:Ag < median	21/26 (80.8%)	1.05 (.26 – 4.19)	13/19 (68.4%)	1.39 (.39 – 5.01)
VWF:Ag < LLN	*1/1 (100%)*		*2/2 (100%)*	

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

above 100% (122.4%), whereas the median VWF:Ag level was below 100% (90%).

When looking at the combination of FXI activity and VWF:Ag coagulation levels, there was a non-significant trend in the endometrial ablation group towards lower success rates when coagulation factor levels were lower. This trend was not seen in the LNG-IUS group (Table 2).

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% vs. 96.0%; OR .08, 95% CI .01 – .68). 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 2).

In this exploratory 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. 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.[11] Increased fibrinolytic activity in the endometrium could play a role.[12] However, it is unclear how this would impact the effectiveness of endometrial ablation but not that of the LNG-IUS. Previous research into the association between decreased coagulation levels and the treatment effect of the LNG-IUS or endometrial ablation was limited to small cohorts describing the effect of a single intervention in women with diagnosed coagulation disorders.[13,14] 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 warfarin use).[15] Ours is the first study exploring the relation between actual coagulation levels and effect of HMB treatment.

We found remarkably lower prevalence numbers of deceased coagulation than earlier studies (4% for decreased FXI and 13% for VWD).[4,5] The probable explanation for this is that we included patients from primary and routine gynaecological care. Therefore, 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 ≥34 years old with HMB. Our assessment of decreased coagulation factors is based on a single measurement. Another limitation is that 10% of women in our study used estrogens at baseline, which can raise VWF blood levels. This may have led to an underestimation of the prevalence of decreased VWF:Ag levels. 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 hypothesised an effect of coagulation factors over their full range. Also, the number of patients with coagulation levels below the LLN (actual number: 0–2 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.

In conclusion, we measured VWF and FXI in participants in a RCT comparing endometrial ablation and LNG-IUS. In this exploratory study, endometrial ablation was associated with fewer successful outcomes in women with low FXI compared to high FXI activity. There were no differences in treatment success between higher and lower VWF levels in both the LNG-IUS and endometrial ablation group. Further research is needed to confirm our findings and to investigate the underlying mechanism, before FXI measurements should be ordered routinely in this setting.

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.

ACKNOWLEDGEMENTS

We thank J.H.A. van Miert for his expertise and methodological advice during statistical analyses. The MIRA trial was funded by ZonMw, the Dutch Organisation for Health Research and Development (grant number: 171202001). No funding was obtained to support this exploratory observational study.

CONFLICT OF INTERESTS

K. Meijer received research grants from Bayer, Pfizer and Sanquin, speaker fees from Aspen, Bayer, BMS, Boehringer Ingelheim, Sanquin and consulting fees from Uniqure. The other authors state that they have no conflicts of interest to declare.

AUTHOR CONTRIBUTION

M. J. van den Brink, S. Wiewel-Verschueren, J.H. Dekker, and K. Meijer contributed to the concept and design of the study; M. J. van den Brink, S. Wiewel-Verschueren, and P. Beelen generated data; M.V. Lukens supervised laboratory analyses; M. J. van den Brink, J. W. van Borselen, J.H. Dekker, and K. Meijer performed statistical analyses and/or interpreted data; M. J. van den Brink and K. Meijer drafted the manuscript; S. Wiewel-Verschueren, P. Beelen, J. W. van Borselen, M.V. Lukens, M.Y. Bongers, and J.H. Dekker critical revised the manuscript.

DATA AVAILABILITY STATEMENT

If desired, we can submit an overview of the data underlying the article.

Marian J. van den Brink[1]
Sophie Wiewel-Verschueren[2,3]
Pleun Beelen[4,5]
Joep W. van Borselen[2]
Marlies Y. Bongers[5,6]
Michaël V. Lukens[7]
Janny H. Dekker[1]
Karina Meijer[2]

[1] *Department of General Practice and Elderly Care Medicine, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands*
[2] *Department of Haematology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands*
[3] *Department of Obstetrics and Gynaecology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands*
[4] *Department of General Practice, Maastricht University, Maastricht University Medical Centre, Maastricht, The Netherlands*
[5] *Department of Obstetrics and Gynaecology, Máxima Medical Centre, Veldhoven, The Netherlands*
[6] *Grow Research School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands*

[7] *Department of Laboratory Medicine, University Medical Centre Groningen, Groningen, The Netherlands*

Correspondence
Karina Meijer, Department of Haematology, HPC DA21, University Medical Centre Groningen, PO Box 30 001, Groningen 9700 RB, The Netherlands.
Email: k.meijer@umcg.nl

ORCID

Marian J. van den Brink https://orcid.org/0000-0001-9805-5015
Sophie Wiewel-Verschueren https://orcid.org/0000-0002-7614-0021
Pleun Beelen https://orcid.org/0000-0002-4196-6835
Joep W. van Borselen https://orcid.org/0000-0003-3661-6707
Marlies Y. Bongers https://orcid.org/0000-0001-9276-9148
Janny H. Dekker https://orcid.org/0000-0001-5005-9324
Karina Meijer https://orcid.org/0000-0001-9447-0465

REFERENCES

1. De Wee EM, Knol HM, Mauser-Bunschoten EP, et al. Gynaecological and obstetric bleeding in moderate and severe von willebrand disease. *Thromb Haemost*. 2011;106(5):885-892.
2. Saes JL, Verhagen MJA, Meijer K, et al. Bleeding severity in patients with rare bleeding disorders: real-life data from the RBiN study. *Blood Adv*. 2020;4(20):5025-5034.
3. Kadir RA, Economides DL, Sabin CA, Pollard D, Lee CA. Assessment of menstrual blood loss and gynaecological problems in patients with inherited bleeding disorders. *Haemophilia*. 1999;5(1):40-48.
4. Shankar M, Lee CA, Sabin CA, Economides DL, Kadir RA. Von willebrand disease in women with menorrhagia: a systematic review. *BJOG*. 2004;111(7):734-740.
5. Knol HM, Mulder AB, Bogchelman DH, Kluin-Nelemans HC, Van Der Zee AGJ, Meijer K. The prevalence of underlying bleeding disorders in patients with heavy menstrual bleeding with and without gynecologic abnormalities. *Am J Obstet Gynecol*. 2013;209(3):202.e1-202.e7.
6. Ray S, Ray A. Non-surgical interventions for treating heavy menstrual bleeding (menorrhagia) in women with bleeding disorders. *Cochrane Database Syst Rev*. 2016;11:CD010338.
7. Demers C, Derzko C, David M, Douglas J. 163-gynaecological and obstetric management of women with inherited bleeding disorders. *J Obstet Gynaecol Can*. 2018;40(2):e91-e103.
8. Beelen P, van den Brink MJ, Herman MC, et al. Levonorgestrel releasing intrauterine system versus endometrial ablation for heavy menstrual bleeding. *Am J Obstet Gynecol*. 2020.
9. Higham JM, O'brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol*. 1990;97(8):734-739.
10. Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2016(1):CD003855.
11. Duga S, Salomon O. Factor XI deficiency. *Semin Thromb Hemost*. 2009;35(4):416-425.
12. Gidley GN, Holle LA, Burthem J, et al. Abnormal plasma clot formation and fibrinolysis reveal bleeding tendency in patients with partial factor XI deficiency. *Blood Adv*. 2018;2(10):1076-1088.
13. Chi C, Huq FY, Kadir RA. Levonorgestrel-releasing intrauterine system for the management of heavy menstrual bleeding in women with inherited bleeding disorders: long-term follow-up. *Contraception*. 2011;83(3):242-247.
14. Huq FY, Al-Haderi M, Kadir RA. The outcome of endometrial ablation in women with inherited bleeding disorders. *Haemophilia*. 2012;18(3):413-420.
15. El-Nashar SA, Hopkins MR, Barnes SA, et al. Health-related quality of life and patient satisfaction after global endometrial ablation for menorrhagia in women with bleeding disorders: a follow-up survey and systematic review. *Am J Obstet Gynecol*. 2010;202(4):348.e1-348.e7.