International Journal of Epidemiologic Research
doi:10.34172/ijer.2020.29 2020 Autumn;7(4):163-166 http://ijer.skums.ac.ir

Original Article

Prevalence of Von Willebrand Disease in Women of Reproductive Age With Heavy Menstrual Bleeding in Kashan, Iran, During 2019

Tahereh Abdoli[1,2*], Mansooreh Samimi[3], Fatemeh Atoof[2,4], Mohammad Shayestehpour[2,5], Majid Ehsani[1,2]

[1]Department of Internal Medicine, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran
[2]Autoimmune Diseases Research Center, Kashan University of Medical Sciences, Kashan, Iran
[3]Department of Gynecology and Obstetrics, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran
[4]Department of Epidemiology and Biostatistics, School of Health, Kashan University of Medical Sciences, Kashan, Iran
[5]Department of Microbiology and Immunology, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran

*Corresponding Author:
Tahereh Abdoli,
Tel: +98-31-55540026-5573,
Email: tabdoli1356@gmail.com

Received: 18 May 2020
Accepted: 19 Sep. 2020
ePublished: 30 Dec. 2020

Abstract

Background and aims: *Von Willebrand disease* (VWD) is an inherited disorder of blood clotting in humans. The prevalence of VWD is different among various populations. The prevalence of this disorder in women with menorrhagia is less reported in Asia and Iran. The present study aimed to determine the prevalence of VWD in women of reproductive age with heavy menstrual bleeding (HMB).

Materials and Methods: A total of 160 women in the reproductive age group (15-45 years) with HMB who referred to the hematology clinic of Kashan Shahid Beheshti hospital during 2019 participated in this cross-sectional study. Demographic characteristics, clinical testing, and physician-reported problems of each participate including age, menstrual cycle length, uterine myoma, and polyp were collected using a questionnaire, sonography, and physical examination of women by a physician. The laboratory tests included hemoglobin (Hb), *ferritin,* iron, and total iron-binding capacity (TIBC).

Results: Fifteen patients (9.3%) with severe menstrual bleeding had VWD with a mean age of 34.60±6.85 years. The frequency of the *uterine fibroid* (*myoma*) in women with VWD was significantly higher than that in patients without VWD (*P*=0.03). The mean ferritin level among 15 women with VWD and 145 women without VWD was 23±4.28 ug/dL and 30.68±4.46 ug/dL, respectively (*P*=0.001). The mean serum iron in total participants was 35.3±11.48 ug/dL and VWD patients had a lower iron level compared to those without VWD (*P*=0.001). There was not a significant difference in TIBC level between women with and without VWD (*P*=0.6).

Conclusion: Based on the results, 9.3% of women of reproductive age with HMB in Kashan, Iran, had VWD, which is lower compared to other regions of Asia.

Keywords: Prevalence, Menorrhagia, Von Willebrand disease

Introduction

*V*on Willebrand disease (VWD) is an inherited disorder of blood clotting caused by a defect or deficiency in von Willebrand factor (VWF).[1] Von Willebrand factor contributes to the localization of platelets at the bleeding site; therefore, it is a key coagulant protein for initiation of hemostasis.[2] The overall prevalence of VWD in the general population is 1%–2%. Men and women are equally affected by this disorder; however, more women are diagnosed with VWD than men because of the menstrual bleeding and childbirth.[3] There are three major forms of VWD. About 75% of all cases of the disease are usually mild, which are categorized as type 1. The VWF works correctly, but its level in the blood of these patients ranges from 20% to 50% of that of normal people; this level is not adequate to control bleeding. A qualitative deficiency of VWF can be found in patients with type 2 VWD, while patients with type 3 VWD have a quantitative deficiency. People with type 3 VWD have little or no VWF in their blood. Type 3 VWD is less common and more severe than type 2 disease. VWF levels can be influenced by several factors including age, race, gender, thyroid function, exercise, stress, and blood group.[4-6]

Women usually lose 30–40 mL of blood during a menstrual cycle. Heavy menstrual bleeding (HMB) or menorrhagia is a menstrual blood loss of ≥60–80 mL per cycle. HMB affects 25% of women in the 30 to 50 years age group and increases with age.[5,7] It is a common problem for women during their reproductive years. More than 50% of cases have an unknown cause; however, HMB can be associated with other disorders such as hypothyroidism, endometriosis, endometritis,

endometrial polyps, polycystic ovary syndrome, uterine fibroids, uterine/cervical malignancy, and VWD.[8] A study showed that only 4% of gynecologists routinely considered VWD in the differential diagnosis in women of reproductive age.[9] Undiagnosed VWD can lead to serious problems including impairment of the quality of life during menses, anemia, and surgical procedures. Previous studies have shown that 78%-92% of women with VWD suffer from HMB,[10,11] compared with a prevalence of 24R-55% in Iranian women of reproductive age.[12]

The prevalence of VWD varies among different populations.[12] The majority of studies were designed to estimate the prevalence of VWD in women with menorrhagia living in European and American countries, and reports from Asia are limited.[5] The prevalence of VWD was reported to be 13% in Ireland,[13] 13% in the UK,[14] 20% in Sweden,[15] 5.1%-17% in the USA,[16] and 16.1% in Taiwan.[17] In addition, there are only two studies with a small sample size that have reported the rate of VWD in women of childbearing age with HMB in Iran.[9,12] Knowing the prevalence of VWD helps clinicians to improve the quality of women's life by diagnosing the cause of HMB on time. There are no data on the prevalence of VWD in Kashan. Therefore, this study was conducted for the first time to determine the prevalence of VWD in women of reproductive age with severe menstrual bleeding in Kashan, Iran, during 2019.

Materials and Methods

Study Population

A total of 160 women in the reproductive age group of 15-45 years with severe menstrual bleeding who referred to the hematology clinic of Kashan Shahid Beheshti hospital during 2019 participated in this cross-sectional study. All subjects signed an informed written consent form. This study was approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1397.104). Patients known to have renal or gastrointestinal disease, major thalassemia, sickle-cell anemia, vitamin B12 deficiency, and women who used anticoagulants or drugs containing estrogen or progestin were excluded from the study.

Data Collection and Laboratory Tests

Demographic characteristics, clinical testing, and physician-reported problems were collected using a researcher-made questionnaire. Clinical problems such as uterine myoma and polyp were diagnosed by a physician based on sonography, history, and physical exam. The laboratory tests included hemoglobin (Hb), ferritin, iron, and total iron-binding capacity (TIBC). Blood samples for the Hb test were collected in EDTA tubes and were analyzed using Sysmex system (Sysmex, Kobe, Japan). Ferritin, iron, and TIBC in sera were measured using an auto-analyzer system (Hitachi, Germany) and biochemistry kits (Pars Azmoon Co., Iran). Von Willebrand factor was analyzed using VIDAS VWF kit (BioMérieux, France) according to the manufacturer's protocol. The specificity and sensitivity of this kit were higher than 99%.

Statistical Analysis

All statistical analyses were performed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). Data were represented as mean ± standard deviation or median for continuous variables and frequencies. Categorical variables were compared using chi-square test. Student's t test or Mann-Whitney U test was used for comparison of quantitative parameters between two groups. A P value below 0.05 was considered statistically significant.

Results

The mean age of 160 women who participated in this study was 33.6±9.18 years (Table 1). Fifteen patients (9.3%) with severe menstrual bleeding had VWD with a mean age of 34.60±6.85 years. There was not a significant difference in the mean age of patients with and without VWD (*P*=0.57, Table 1). In clinical examinations, 14 patients were diagnosed with uterine Myoma. The frequency of Myoma among VWD patients was significantly higher than that among patients without VWD (*P*=0.03). The

Table 1. Comparison of Demographic, Clinical and Laboratory Parameters Between Women with and Without VWD

Parameters		Patients With VWD (n=15)	Patients Without VWD (n=145)	*P* Value
Age (mean ± SD)		34.60±6.85	33.50±9.40	0.570
Iron (ug/dL)		13.37±10.49	18.27±4.42	0.001
Ferritin (ug/dL)		23±4.28	30.68±4.46	0.001
Hemoglobin (g/dL) (median)		8.9	11.2	0.001
Menstrual cycle length)Median(		23	25	0.002
TIBC (ug/dL)		347	340	0.600
Myoma	Yes	4 (28.6%)	10 (71.4%)	0.030
	No	11 (7.5 %)	135 (92.5%)	
Polyp	Yes	1 (20%)	4 (80%)	0.390
	No	14 (9 %)	141 (91%)	

uterine polyp was observed in 1 woman with VWD and in 4 women without VWD, but this difference was not statistically significant (*P*=0.39). The median menstrual cycle length in patients with and without VWD was 23 and 25, respectively (*P*=0.002). The mean ferritin level among the total population under study was 29.96±6.67 ug/dL. The difference in the mean ferritin level between women with and without VWD was about 7 ug/dL (Table 1, *P*=0.001). The mean serum iron level in total subjects was 35.3±11.48 ug/dL and VWD patients had a lower iron compared to those without VWD (*P*=0.001). The median Hb level among all patients was 11.1 ug/dL, and this laboratory parameter was lower among women with VWD compared with women without VWD (*P*=0.001). The median TIBC among all participants was 342 ug/dl and it was 347 ug/dl among women with VWD.

Discussion

In the present study, of 160 women with HMB, 9.3% had VWD. The prevalence of VWD has been reported to vary among women suffering from HMB in different regions.[12] It is estimated to be 18% in Europe and 10% in North America.[5] Dilley et al reported VWD in 6.6% of patients with menorrhagia in the USA.[18] Further, in a study by Woo et al, 9% of women with bleeding disorders had VWD.[19] Reports of the prevalence of VWD among women with menorrhagia are limited in Asia and Iran.[3] In a study conducted in Kermanshah, Iran, the *p*revalence of VWD was reported to be 55.3% among 482 women (age group: 19 to 45 years) with menorrhagia.[12] Moreover, it was 24% among women with HMB in Semnan, Iran,[9] which is greater compared to our findings. In some studies, the patients have been selected from specialized centers or anticoagulation clinics; therefore, the population under study and the setting of the studies may account for the higher prevalence in some of the reports. In Pakistan, Borhany et al founded that the VWD, with a prevalence of 21.3%, was the second common bleeding disorder among women with menorrhagia.[20] The prevalence rate of VWD in Taiwan was reported to be about 16% [21], while it was 6% in Hong Kong and 15.62% in India.[5] Previous studies showed that ethnic differences could affect the prevalence rate of VWD in population. Dilley et al reported a VWD prevalence of 16% among white women and 1.4% among black women.[18]

The prevalence of uterine lesions in women with HMB and VWD is less known. In a study, about 50% of women with VWD who were hysterectomized because of menorrhagia had uterine abnormalities.[9] Another study reported that fibroid, ovarian cyst, endometriosis, endometrial hyperplasia, and endometrial polyps were significantly more common in VWD patients than in healthy peoples. In the present study, the frequency of the uterine fibroid (myoma) in women with VWD was significantly higher than that in patients without VWD (*P*=0.03), but the difference in the frequency of the uterine polyp between the two groups was not statistically significant. These findings are compatible with the results of a study by Rahbar et al in Iran.[9] It is more likely that women with menorrhagia and VWD who refer to the clinic undergo gynecological examination. Therefore, VWD may lead to the diagnosis of uterine lesions and reporting the higher frequency of them in affected women. However, proper diagnosis of VWD in patients with HMB can improve the health-related quality of life in women. The present study was limited by the small study population. In addition, this study was a single-institution report.

Conclusion

Results of the current study demonstrated that 9.3% of women of reproductive age with HMB in Kashan had VWD, which is lower compared with other regions of Iran and Asia. Future studies with larger sample sizes from multiple regions are required to evaluate more variables and increase our awareness of VWD prevalence in Asia. Testing for this disorder should be a part of routine examination of women presenting with menorrhagia.

Conflict of Interest Disclosures

The authors have no conflict of interests to declare.

Ethical Approval

This study was approved by Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.MEDNT.REC.1397.104).

Authors' Contributions

ME and MS conceived the idea and study design, TA generated the data, FA analyzed the data, and MSH wrote the paper. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to acknowledge the research deputy at Kashan University of Medical Sciences for their support. We are also thankful to all patients who participated in this study.

Funding

This study was funded by Kashan University of Medical Sciences (grant number: 97166).

References

1. Stufano F, Boscarino M, Bucciarelli P, Baronciani L, Maino A, Cozzi G, et al. Evaluation of the utility of von Willebrand factor propeptide in the differential diagnosis of von Willebrand disease and acquired von Willebrand syndrome. Semin Thromb Hemost. 2019;45(1):36-42. doi: 10.1055/s-0038-1660481.
2. Lukes AS, Kadir RA, Peyvandi F, Kouides PA. Disorders of

hemostasis and excessive menstrual bleeding: prevalence and clinical impact. Fertil Steril. 2005;84(5):1338-44. doi: 10.1016/j.fertnstert.2005.04.061.
3. James AH. Von Willebrand disease in women: awareness and diagnosis. Thromb Res. 2009;124 Suppl 1:S7-10. doi: 10.1016/s0049-3848(09)70151-3.
4. Dorgalaleh A, Tabibian S, Shams M, Ala F, Bahoush G, Jazebi M, et al. Von Willebrand disease in Iran: diagnosis and management. Ann Blood. 2018;3(1):1-11. doi: 10.21037/aob.2018.01.01
5. Shankar M, Lee CA, Sabin CA, Economides DL, Kadir RA. von Willebrand disease in women with menorrhagia: a systematic review. BJOG. 2004;111(7):734-40. doi: 10.1111/j.1471-0528.2004.00176.x.
6. Ng CJ, Di Paola J. Von Willebrand disease: diagnostic strategies and treatment options. Pediatr Clin North Am. 2018;65(3):527-41. doi: 10.1016/j.pcl.2018.02.004.
7. Leebeek FW, Eikenboom JC. Von Willebrand's disease. N Engl J Med. 2016;375(21):2067-80. doi: 10.1056/NEJMra1601561.
8. Janbabaei G, Borhani S, Rashidi M, Farazmandfar T, Shekarriz R, Khademloo M, et al. Frequency of bleeding disorders in women presenting menorrhagia in the north of Iran. Blood. 2011;118(21):4660. doi: 10.1182/blood.V118.21.4660.4660.
9. Rahbar N, Faranoush M, Ghorbani R, Sadr Alsadat B. Screening of von Willebrand disease in Iranian women with menorrhagia. Iran Red Crescent Med J. 2015;17(1):e18244. doi: 10.5812/ircmj.18244.
10. Hallberg L, Högdahl AM, Nilsson L, Rybo G. Menstrual blood loss--a population study. Variation at different ages and attempts to define normality. Acta Obstet Gynecol Scand. 1966;45(3):320-51. doi: 10.3109/00016346609158455.
11. Lukes AS, Kadir RA, Peyvandi F, Kouides PA. Disorders of hemostasis and excessive menstrual bleeding: prevalence and clinical impact. Fertil Steril. 2005;84(5):1338-44. doi: 10.1016/j.fertnstert.2005.04.061.
12. Payandeh M, Rahimi Z, Kansestani AN, Hemmati S, Aleyasin M, Zare ME, et al. Clinical features and types of von Willebrand disease in women with menorrhagia referred to hematology clinic of Kermanshah. Int J Hematol Oncol Stem Cell Res. 2013;7(2):1-5.
13. Woo YL, White B, Corbally R, Byrne M, O'Connell N, O'Shea E, et al. von Willebrand's disease: an important cause of dysfunctional uterine bleeding. Blood Coagul Fibrinolysis. 2002;13(2):89-93. doi: 10.1097/00001721-200203000-00003.
14. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. Lancet. 1998;351(9101):485-9. doi: 10.1016/s0140-6736(97)08248-2.
15. Edlund M, Blombäck M, von Schoultz B, Andersson O. On the value of menorrhagia as a predictor for coagulation disorders. Am J Hematol. 1996;53(4):234-8. doi: 10.1002/(sici)1096-8652(199612)53:4<234::aid-ajh4>3.0.co;2-z.
16. Philipp CS, Dilley A, Miller CH, Evatt B, Baranwal A, Schwartz R, et al. Platelet functional defects in women with unexplained menorrhagia. J Thromb Haemost. 2003;1(3):477-84. doi: 10.1046/j.1538-7836.2003.00061.x.
17. Chen YC, Chao TY, Cheng SN, Hu SH, Liu JY. Prevalence of von Willebrand disease in women with iron deficiency anaemia and menorrhagia in Taiwan. Haemophilia. 2008;14(4):768-74. doi: 10.1111/j.1365-2516.2008.01777.x.
18. Dilley A, Drews C, Miller C, Lally C, Austin H, Ramaswamy D, et al. von Willebrand disease and other inherited bleeding disorders in women with diagnosed menorrhagia. Obstet Gynecol. 2001;97(4):630-6. doi: 10.1016/s0029-7844(00)01224-2.
19. Woo YL, White B, Corbally R, Byrne M, O'Connell N, O'Shea E, et al. von Willebrand's disease: an important cause of dysfunctional uterine bleeding. Blood Coagul Fibrinolysis. 2002;13(2):89-93. doi: 10.1097/00001721-200203000-00003.
20. Borhany M, Shamsi T, Naz A, Farzana T, Ansari S, Nadeem M, et al. Clinical features and types of von Willebrand disease in Karachi. Clin Appl Thromb Hemost. 2011;17(6):E102-5. doi: 10.1177/1076029610387125.
21. Chen YC, Chao TY, Cheng SN, Hu SH, Liu JY. Prevalence of von Willebrand disease in women with iron deficiency anaemia and menorrhagia in Taiwan. Haemophilia. 2008;14(4):768-74. doi: 10.1111/j.1365-2516.2008.01777.x.