Section: Miscellaneous

Original Research Article

EVALUATION AND MANAGEMENT OF PATIENTS WITH MENORRHAGIA AND LOW VON WILLEBRAND FACTOR OR TYPE I VON WILLEBRAND DISEASE WITH HIGH AND LOW DOSE ESTROGEN AND THEIR COMBINATION WITH DDAVP AND/OR AMINOCAPROIC ACID.

Vasundhara P Kailasnath[1], Lathika B Kangila[2], Waseem IqbalKhanday[3]

[1]Department of Pediatric Hematology Oncology & BMT, Fortis Hospital Bannerghatta Road Bangalore, India.
[2]Nura AI Screening Center Bangalore, India.
[3]PG and Research Centre in Biotechnology MGR College Hosur Tamilnadu, India.

Received *: 05/12/2024*
Received in revised form *: 17/01/2025*
Accepted *: 01/02/2025*

Corresponding Author:
Dr.Vasundhara P Kailasnath,
Department of Pediatric Hematology, Oncology & BMT, Fortis Hospital Bannerghatta Road, Bangalore, India.
Email: drvasundhara.kailasnath@gmail.com

DOI:10.70034/ijmedph.2025.1.63

Source of Support: Nil,
Conflict of Interest: Nonedeclared

Int J Med Pub Health
2025; 15 (1); 331-335

ABSTRACT

Background: Menorrhagia is a common symptom in adolescents with Von Willebrand Disease (VWD). Combined oral contraceptive pills (OCP's) are the most common treatment modality for menorrhagia. **Hypothesis:** This study showed response rates of high and low dose estrogen and their use in combination with DDAVP or Amicar in adolescent females with menorrhagia and Type I VWD/ low Von Willebrand Factor (VWF).

Materials and Methods: The patient population consisted of 80 menorrhagia patients aged 9-19. Collected data included age of menarche, onset of menorrhagia, follow up duration, severity of menorrhagia including PBAC score, co-morbidities, and family history of bleeding or clotting disorders, blood group, factor VIII coagulant activity, ristocetin cofactor activity and VW Ag level.

Results: Study showed 38.5% patients were changed from low dose estrogen combined OCP to high dose (50 mcg EE) OCP, 7.7% were changed from high dose estrogen containing combined OCP to a lower dose OCP and 38.5% patients remained unchanged.11.5% patients were switched from combined OCP to progesterone only pills and 3.8% was switched vice-versa.Patients on combined OCP, 25% were on continuous high dose estrogen containing combined OCP, 30% were on cyclic high dose estrogen containing combined OCP 10% were on continuous low dose estrogen containing combined OCP, and 35% on cyclic low dose estrogen containing combined OCP.

Conclusion: Higher dose of estrogen seems to be more effective in controlling menorrhagia in the adolescent population with a low VWF/Von Willebrand disease.

Keywords: Von Willebrand Disease, Menorrhagia, Anti-fibrinolytics, DDAVP.

INTRODUCTION

Von Willebrand Disease (VWD) is one of the most common inherited bleeding disorders in women. About 3 million women in North America are believed to have an inherited bleeding disorder such as VWD or hemophilia. Menorrhagia is often the initial or only symptom in women with VWD.[1,2]The prevalence of VWD in women with menorrhagia is reported to be 17% to 20%, much higher than the reported prevalence of 1-2% in the general population.[3,4,5]Even though significant menorrhagia is seen in majority of females during childhood, there is often a delay in diagnosing VWD.[6]This delay is partly due to failure of physicians to recognize VWD as an important cause

of menorrhagia in adolescents and partly as a result of lack of laboratory expertise regarding coagulation testing and interpretation. Moreover, variance of Von Willebrand Factor (VWF) level with ABO blood groups, hormone levels and stress] compounds this problem.[7,8,9] In one of the surveys, it was found that only 4% of gynecologists routinely considered VWD as a differential in an adolescent girl with menorrhagia versus 91% of hematologists with expertise in hemostasis.[10,11] Women with VWD are more susceptible to severe bleeding episodes when compared to men, due to challenges of menstruation and pregnancy.[12] Menorrhagia is defined as menstrual blood loss of more than 80 ml/cycle over several consecutive cycles. Mechanisms and causes of menorrhagia vary with age.[13]For instance, in adolescent females, heavy irregular uterine bleeding in the first one to two years after menarche is attributed to anovulation due to immaturity of the hypothalamic-pituitary-ovarian axis.[14,15] However, VWD is the etiology in 15% of females with a history of menorrhagia without a clear cut etiology.[16]Though the prevalence of menorrhagia in adolescent females with VWD is high, no guidelines exist regarding specific treatment modalities.[17] Although combined oral contraceptive pills (OCP) are the most common treatment modality for menorrhagia, randomized controlled studies to assess their efficacy are lacking. Data on response rates to different doses and combinations of estrogens and progestins in OCP, and data on response rates to combined therapy of OCP with desmopressin acetate (DDAVP) and/or epsilon aminocaproic acid (Amicar) and/or von Willebrand factor/factor VIII concentrates are also sparse. In most centers, adolescents with menorrhagia who have bleeding disorders are co-managed by hematologists and gynecologists separately which is a big inconvenience to the patients and their families as the treatments require frequent changes, both by hematologists as well as gynecologists. Keeping this in mind, we attempted to create a multidisciplinary clinic at our Hemophilia Treatment Center. In this study, we present response rates of high and low dose estrogen and their combination with DDAVP and/or Amicar in adolescent females that presented with menorrhagia and either Type I VWD or low VWF (see definition in the methods section) to our Multidisciplinary Hematology/Gynecology Clinic at the Hemophilia Treatment Center.

MATERIALS AND METHODS

The patient population consisted of 80 patients aged 9-19 years, who were primary referrals to a Multidisciplinary Hematology/Gynecology clinic for evaluation of menorrhagia. A retrospective chart review was completed on these patients following an Institutional Review Board (IRB) approval. Collected data included age of menarche, onset of menorrhagia, follow up duration, severity of menorrhagia including PBAC score, co-morbidities, and family history of bleeding or clotting disorders, blood group, factor VIII coagulant activity, ristocetin cofactor activity, and VW Ag level. The new guidelines published by the National Heart, Lung and Blood Institute strictly define VWD by a ristocetin cofactor level of were used. Choice of the dose of estrogen in the combination pills was provider dependent as there were two gynecologists involved in the care of these patients. Choice of cyclic versus continuous OCP use was also provider dependent. Patients on cyclic OCP's had a week of placebo pills in every 28-day pack whereas patients on the continous OCP's skipped the week of placebo pills. DDAVP or Amicar were used alone if patient's or their parents refused OCP's initially. Combination of OCP's and DDAVP and/or Amicar was used in patients who did not have symptomatic relief with OCP's alone. Brand of OCP's and/or dose of estrogen were changed prior to adding DDAVP and/or Amicar to the regimen. Choice of DDAVP over Amicar in combination with OCP's was provider and somewhat patient dependent. Von Willebrand factor/factor VIII concentrates were used only if all above modalities failed.

RESULTS

Of the 80 patients with menorrhagia, 26 patients (32.5%) had ristocetin co factor activity 100 indicating it was significant menorrhagia. All of the 26 patients with VWD type I/low VWF had an ultrasound of abdomen and pelvis done which showed 2(7.7%) patients with ovarian cysts and the remainder 24 patients (92.3%) with a normal ultrasound. The demographic analysis of patient population summarized in Table 1.

During the course of the study, 10 (38.5%) patients were changed from low dose estrogen (<=35 mcg ethinyl estradiol (EE)) combined OCP to high dose (50 mcg EE) OCP, 2 (7.7%) were changed from high dose estrogen containing combined OCP to a lower dose OCP. Ten (38.5%) patients remained on the same dose of combined OCP or progesterone only pills. Three (11.5%) pts were switched from combined OCP to progesterone only pills and 1 (3.8%) was switched vice-versa as summarized in Table 2. Of the 20 patients on combined OCP, five (25%) were on continuous high dose estrogen containing combined OCP, six (30%) were on cyclic high dose estrogen containing combined OCP, two (10%) were on continuous low dose estrogen containing combined OCP, and seven (35%) on cyclic low dose estrogen containing combined OCP as shown in Table 3. In our study population 54% of our patients achieved bleeding control with hormonal therapy alone and 46% required the combination hormonal therapy with DDAVP, Amicar or Humate P as described in Table 5.

Table 1: Demographic analysis of the patient population

Total number of patients	N =80	
VWD	n=26	32.5%
Platelet dysfunction	n=1	1.3%
Menorrhagia + MR+ CP-Hysterectomy	n=1	1.3%
Menorrhagia + Protein c def	n=2	2.5%
Age at menarche(yrs)(Mean ± SD)	11.31±1.54	
Age at diagnosis of menorrhagia (yrs) (Mean ± SD)	12.65±1.77	
Follow up period(yrs)		
Mean	1.73	
Range	0.2 - 3	
Severity	N=11	
PBAC Score >100	n= 11	
Co morbidities	N=26	38.5%
Hypothyroidism	n= 2	
Migraine	n= 4	
Ovarian cyst	n= 2	
Seizure	n=2	
Ultrasonography	N=26	92.3%
Normal	n= 24	
OC	n= 2	
Blood type	N=26	
O	n= 19	73.1%
A	n= 4	15.4%
B	n= 3	11.5%
Family History	N= 26	
Menorrhagia/bleeding	n= 9	34.6%
Clots/DVT	n= 7	26.9%

Table 2: Treatment response to various dosages of hormonal therapies

Treatment	N=26	% of response
Low dose Estrogen to high dose Estrogen	N =10	38.5%
20-50	n =1	
30-50	n =9	
Higher dose Estrogen to low dose Estrogen 30-20	N =2	7.7%
	n =2	
Stayed On	N =10	38.5%
Estrogen 30	n =6	
Estrogen 50	n =3	
Progesterone	n =1	
Change Estrogen to Progesterone	n =3	11.5%
Change Progesterone to Estrogen	n =1	3.8%

Table 3: Continuous and cyclic hormonal treatment

Treatment	N=20	% of response
Continuous High doseEstrogen	n =5	25%
Cyclic High doseEstrogen	n =6	30%
Continuous Low doseEstrogen	n =2	10%
Cyclic Low doseEstrogen	n =7	35%

Table 4: Optimal treatment regimen

Current treatment	N=26	% of response
Estrogen	n =8	30.7%
Patch	n=2	7.6%
Progestrone	n=3	11.5%
Depo	n=1	3.8
Estrogen + DDVAP	n =8	30.7%
Estrogen + Amicar	n =3	11.5%
Estrogen + DDVAP + Humate P	n =1	3.8%

DISCUSSION

Treatment of menorrhagia in adolescents with VWD is complex. A combination of therapies is usually required for symptomatic relief and improving quality of life. Even though medical management is first line for treatment of menorrhagia, there is lack of prospective data on the efficacy of commonly used medical therapies. To our knowledge, there are no published guidelines for a stepwise approach in the choice of treatment modalities available to treat menorrhagia in this population. In our retrospective analysis, the prevalence of VWD was 32.5%. We used a more liberal definition of VWD as a ristocetin co-factor activity of 57 IU/dl or less. Most studies evaluating the prevalence of menorrhagia in VWD have repoprted a range of 3-36% depending on the definition of VWD used and clinical setting used (e.g. primary care office, inpatients, or hemophilia treatment center).[18,19,20,21,22,23,24,25]Our

patient population is mainly comprised of patients who would be described to have a 'low VWF level'. In our study, patients on high dose estrogen had a better clinical response rate compared to patients on low dose estrogen or on progesterone only OCP as summarized in Table 2. Oral contraceptives in women with VWD reduce menstrual blood loss and possibly increase VWF and factor VIII levels.[26,27,28,29]There is no available data at this time to recommend one type of Combination OCP over another as no randomized controlled trials exist regarding this issue. It is possible that the dose of estrogen is directly responsible for the amount of rise in VWF and its activity, though this has not been proven.Nevertheless, a higher dose of estrogen for an extended period of time has to be balanced with the increased risk of blood clots and other side effects. Our study could not assess the frequency of side effects and tolerability of high dose estrogen in this population due to small number of patients. A majority of our patients were on cyclic combination OCP including both the low dose and the high dose estrogen combinations. A recent study reported sixty-five percent of girls on combination OCP preferred the use of extended cycle pills (63-84 days of active pills) despite the occasional breakthrough bleeding that may occur.[25] Half of our patients achieved bleeding control with hormonal therapy alone, whereas the rest required a combination of OCP with DDAVP, Amicar, or both described in Table 5. Hemostatic therapies such as DDAVP and/or Amicar or tranexamic acid (more recently available in the US) are usually considered in those adolescents who have had a proper gynecologic evaluation and failed hormonal management. Some reports of their use alone and in combination with hormonal methods demonstrating equal effectiveness and safety profile exist in the literature.[30]More data (and prospective studies) are clearly needed to evaluate the safety and efficacy of these combinations in this patient population. A recent multisite, prospective, crossover study demonstrated that while both DDAVP and tranexamic acid reduce menstrual flow in women with bleeding disorders, tranexamic acid was more effective at decreasing PBAC score.[31]Tranexamic acid was not available to us during the time of conducting this study. An interesting proposal would be to randomize the hemostatic agents (DDAVP/Amicar/Tranexamic acid) with OCP upfront in the management of adolescents with menorrhagia. Our small study does have notable limitations. First, we did not have uniform assessment of menorrhagia using an objective tool such as PBAC score in all patients. Secondly, the small sample size precludes us from making meaningful statements about the safety and efficacy of combining multiple modalities for better control of menorrhagia. While Levonorgestrel-containing intrauterine devices (LNG) are a newer successful treatment modality for menorrhagia, a comparison of LNG is not included as the device was not commonly used in adolescents at the time of this evaluation.[32] Lastly, quality of life assessment was not done as part of this study. However, this study does add fuel to the fire of the need for prospective randomized controlled studies of the various modalities, hormonal as well as non-hormonal, in the management of an adolescent with menorrhagia in summary, we conclude that a higher dose of estrogen seems to be more effective in controlling menorrhagia in the adolescent population with a low VWF/Von Willebrand disease. Combination of hormonal methods with hemostatic agents such as DDAVP and/or Amicar may be needed in some situations. Prospective studies are however needed to confirm these findings and to evaluate the safety and efficacy of these agents either alone or in combination so that clinically useful step-wise approaches can be developed to manage menorrhagia in the adolescent population with a bleeding disorder.

CONCLUSION

Higher dose of estrogen appeared to be more effective in controlling menorrhagia in the adolescent population with a low VWF/Von Willebr and disease. Combination of hormonal methods with hemostatic agents such as DDAVP and Amicar may be needed in some circumstances.

Acknowledgement: We are thankful to doctor Sanjay P Ahuja for his contribution.

Financial support and sponsorship: Nil.

Conflict of interest: There is no conflict of interest.

REFERENCES

1. Sadler JE, Mannucci PM, Berntorp E. Impact, diagnosis and treatment of von Willebranddisease.ThrombHaemost 2000; 84: 160–7.
2. Ragni MV, Bontempo FA, Hassett AC. Von Willebrand disease and bleeding in women. Haemophilia1999; 5: 313-7.
3. Quiroga T, Goycoolea M, Panes O, Aranda E, Martínez C, Belmont S, Muñoz B, Zúñiga P, Pereira J, Mezzano D. High prevalence of bleeders of unknown cause among patients with inherited mucocutaneousbleeding.A prospective study of 280 patients and 299 controls. Haematologica. 2007 Mar; 92: 357-65.
4. Edlund M, BlombackM, von Schoultz B, AnderssonO.On the value of menorrhagia as a predictor for coagulation disorders. Am J Hematol 1996; 53: 234–238.
5. KujovichJ.VonWillebrand's Disease and Menorrhagia: Prevalence, Diagnosis and Management. American Journal of Hematology 2005; 79: 220–228
6. Kirtava A, Crudder S, DilleyA. Lally C, Evatt B. Trends in clinical management of women with von Willebrand disease: a survey of 75 women enrolled in haemophilia treatment centres in the United States. Haemophilia 2004; 10: 158–161.
7. Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ, Montgomery RR.The effect of ABO blood group on the diagnosis of von Willebrand disease. Blood 1987; 69:1691.
8. Mandalaki T, Louizou C, Dmitriadou C, Symeonides PH. Variations in factor VIII during the menstrual cycle in normal women. N Engl J Med 1980; 302: 1093.
9. Rickles FR, Hoyer LW, Rick ME, Ahr DJ. The effects of epinephrine infusion in patients with von Willebrand disease. J Clin Invest 1976; 57: 1618.

10. Dilley A, Drews C, Lally C, Austin H, Barnhart E, Evatt B. A survey of gynecologists concerning menorrhagia: perceptions of bleeding disorders as a possible cause. J Womens Health Gend Based Med 2002; 11: 39–44.
11. Cohen AJ, Kessler CM, Ewenstein BM. Management of von Willebrand disease: a survey on current clinical practice from the haemophiliacentres of North America. Haemophilia 2001; 7: 235–24.
12. Greer IA, Lowe GD, Walker JJ, Forbes CD. Hemorrhagic problems in obstetrics and gynecology in patients with congenital coagulopathies. Br J ObsetGynecol 1991; 98: 909–18.
13. Brenner PF. Differential diagnosis of abnormal uterine bleeding.Am J Obstet Gynecol. 1996; 175: 766–769.
14. Neinstein LS. Menstrual problems in adolescents.Med Clin North Am 1990; 74: 1181–1203.
15. Hertweck SP. Dysfunctional uterine bleeding.ObstetGynecolClin North Am. 1992; 19:129–149.
16. Kadir RA, Economides DL, Sabin CA, et al. Frequency of inherited bleeding disorders in women with menorrhagia. Lancet 1998; 351: 485-489.
17. Nichols WL, HultinMB,James AH, et al von Willebrand disease (VWD): evidence based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). Haemophilia 2008; 14, 171–232.
18. Phillipp CS, Faiz A, Dowling N et al. Age and the prevalence of bleeding disorders in women with menorrhagia. ObstetGynecol 2005,1051:61-6.
19. Claessens EA, Cowell CA. Acute adolescent menorrhagia. Am J ObstetGynecol 1981;139:277-80.
20. Smith YR, Quint EH, Hertzberg RB. Menorrhagia in adolescents requiring hospitalization.J PediatrAdolescGynecol 1988; 11:13-5.
21. Oral E, Cagdas A, Gezer A et al. Hematological abnormalities in adolescent menorrhagia. Arch GynecolObstet 2002; 266:72-4.
22. Bevan JA,Maloney KW, Hillery CA et al. Bleeding disorders:a common cause of menorrhagia in adolescents. J Pediatr 2001;138 :856-61.
23. Jayasinghe Y, Moore P, Donath S et al. Bleeding disorders in teenagers presenting with menorrhagia. AustN Z J ObstetGynaecol 2005; 45:439-43.
24. Mikhail S, Varadarajan R, Kouides P. The prevalence of disorders of haemostasis in adolescents with menorrhagia referred to a haemophilia treatment centre. Haemophilia 2007; 13:627-32.
25. Chi C, Pollard D, Edward GD et al Menorrhagia in adolescents with inherited bleeding disorders. J PediatrAdolescGynecol 2010; 23:215-32.
26. Foster PA. The reproductive health of women with von Willebrand disease unresponsive to DDAVP: results of an international survey. On behalf of the Subcommittee on von Willebrand Factor of the Scientific and Standardization Committee of the ISTH. ThrombHaemost 1995; 74:784-90.
27. Beller FK, Ebert C. Effects of oral contraceptives on blood coagulation.A review. ObstetGynecolSurv 1985; 40:425-36.
28. Kadir RA, Economides DL, Sabin CA et al. Variations in coagulation factors in women: effects of age, ethnicity, menstrual cycle and combined oral contraceptive. ThrombHaemost 1999; 82:1456-61.
29. Middeldorp S, Meijers JC, Van den Ende. Effects on coagulation of levonorgestrel- and desogestrel-containing low dose oral contraceptives: a cross over study. ThrombHaemost 2000; 84:4-8.
30. Amesse LS, Pfaff-Amesse T, Leonardi R. Oral contraceptives and DDAVP nasal spray: patterns of use in managing vWD-associated menorrhagia: a single institution study. J PediatrHematolOncol 2005; 27: 357-363.
31. Kouides PA, Byams VR, Phillip CS. Multisite management study of menorrhagia with abnormal laboratory haemostasis: a prospective crossover study of intranasal desmopressin and oral tranexamic. Br J Haematol 2009; 145: 212-20.
32. Kingman CE, Kadir RA, Lee CA et al. The use of levonorgestrel-releasing intrauterine system for treatment of menorrhagia in women with inherited bleeding disorders. BJOG 2001;111: 1425-8.