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Complications of hysterectomy in women with von Willebrand disease

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Summary

Case reports and small case series suggest that women with von Willebrand disease (VWD) are at a very high risk of bleeding complications with hysterectomy. As the procedure may be beneficial to women who suffer from heavy menstrual bleeding and have completed childbearing, an understanding of the true risks involved is essential for appropriate decision making. To estimate the incidence of bleeding and other complications in women with VWD who undergo hysterectomy. The United States Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality for the years 1988–2004 was queried for all hysterectomies for non-malignant conditions. Data were analysed based on the NIS sampling design. Bivariate analyses were used to examine the differences between women with and without VWD. Multivariate analysis was used to adjust for potential confounders among women who underwent hysterectomy for heavy menstrual bleeding. 545 of the 1 358 133 hysterectomies were to women with VWD. Women with VWD were significantly more likely to experience intraoperative and postoperative bleeding (2.75% vs. 0.89%, $P < 0.001$) and require transfusion (7.34% vs. 2.13%, $P < 0.001$) than women without VWD. One woman with VWD died. While the risk of bleeding complications from hysterectomy in women with VWD is smaller than previously reported, women with VWD did experience significantly more bleeding complications than women without VWD. Nonetheless, for women who have completed child-bearing, the risks of hysterectomy may be acceptable.

Keywords

hysterectomy; menorrhagia; von Willebrand disease

Introduction

von Willebrand disease (VWD) is the most common inherited bleeding disorder. Menorrhagia or heavy menstrual bleeding is the most common symptom women with VWD experience, affecting up to 100% of women who have the condition [1–11]. Consequently, women with VWD are more likely to undergo hysterectomy and undergo the procedure at a younger age than women without VWD. Among 102 women with VWD surveyed by the United States Centers for Disease Control and Prevention (CDC), 26% had undergone hysterectomy compared with 9% of age-matched controls [6]. On the other hand, women

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who have completed childbearing and might benefit from the operation, may be denied the procedure out of fear of bleeding complications. Previous data about the procedure in women with VWD are very limited and are based on case reports and small case series with uncertain case ascertainment. These data suggest that women with VWD are at a very high risk of bleeding complications with hysterectomy. The rate of bleeding complications in these series has been reported to be 3/5 or 60% (95% confidence interval of 17–99%) [11], 2/7 or 29% (95% confidence interval of 0.1–62%) [3] and 4/18 or 22% [10]. There are no large epidemiological studies of hysterectomy in women with VWD, yet an understanding of the risks involved is essential for patients to make an informed decision about the procedure and for physicians to counsel their patients appropriately.

von Willebrand disease is a relatively rare condition. No one medical centre has a sufficiently large number of patients to obtain meaningful estimates of their frequency of the diagnosis of VWD among women undergoing hysterectomy or the incidence of bleeding complications. The purpose of this study was to use a large national database to estimate the incidence of bleeding and other complications in women with VWD undergoing hysterectomy.

Methods

Study population

The research protocol used in this study was reviewed and approved by the Duke University Medical Center Institutional Review Board. The Nationwide Inpatient Sample (NIS), from the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ) was queried for all discharge codes including hysterectomy for the years 1988–2004 (the latest data available at the inception of the study). The NIS contains data from approximately 1000 hospitals and is the largest all-payer inpatient care database in the United States (US). The NIS is a 20% stratified sample (multi-staged cluster sample) from a sampling frame that comprises 90% of all US hospital discharges. Included in the sample are general hospitals and academic medical centres [12,13]. Rehabilitation hospitals, long-term hospitals, psychiatric hospitals and alcoholism or chemical dependency treatment facilities are excluded. The hospitals are divided into strata based on ownership, bed size, teaching status, urban vs. rural location and region. Sampling probabilities are proportional to the number of hospitals in each stratum.

Information included in the NIS is what can be derived from a typical discharge abstract, with safeguards to protect the privacy of individual patients, physicians, and hospitals. These data include primary and secondary diagnoses; primary and secondary procedures; admission and discharge status; demographic information such as gender, age, race and median income for ZIP Code; expected payment source; total charges; length of stay and hospital characteristics. Although the data are limited to the information described above, the NIS is the most reliable source of US data on hospital admissions and discharges. Reliability is supported by agreement between the NIS, a telephone survey and the National Health Interview Survey (a national, door-to-door survey). Invalid or inconsistent diagnostic codes are flagged and dealt with by the HCUP [12,13]. Missing data were excluded from this analysis.

Subjects who had a hysterectomy for a benign gynaecological condition were identified from NIS records for 1988–2004 using the International Classification of Diseases Ninth Revision (ICD-9) codes 68.3 (subtotal abdominal hysterectomy), 68.4 (total abdominal hysterectomy), 68.5 (vaginal hysterectomy), 68.51 (laparoscopically assisted vaginal hysterectomy) or 68.59 (other and unspecified hysterectomy). Results were not stratified by type of hysterectomy, but subjects who had a hysterectomy for an obstetric or a malignant

condition were excluded. Records with the code 68.8 (pelvic evisceration), 68.6 (radical abdominal hysterectomy) and 68.7 (radical hysterectomy) were excluded, as were any records which included the code 180 (malignant neoplasm of cervix uteri), 181 (malignant neoplasm of placenta), 182 (malignant neoplasm of body of uterus), 183 (malignant neoplasm of ovary and other uterine adnexa and 184 (malignant neoplasm of other unspecified female genital organs). Records with a code for delivery or obstetrical operation, codes 72–75, were also excluded.

Study design

The ICD-9 code used for VWD was 286.4. The code does not allow for the further classification of VWD by type, severity or level of von Willebrand factor. Age, race, income, reason for hysterectomy, intraoperative and postoperative complications, transfusion, infection, other wound complications, thrombotic events, length of stay and cost of hospitalization at the time of hysterectomy were compared between women with a diagnosis of VWD and women without. Transfusion included packed red cells, platelets and coagulation factors including, possibly, von Willebrand factor or factor VIII concentrates, but did not include hemostatic medications such as 1-deamino-8-D-arginine vasopressin or antifibrinolytic medication.

Statistical analysis

Data were analysed based on the NIS sampling design, a multi-staged sampling frame consisting of three stages. The three stages are (i) strata (geographic region, urban vs. rural location, teaching status, type of ownership and bed size), (ii) hospitals within the strata and (iii) individual discharges weighted by population counts and controlled for missing data. STATA 9.0 (Stata Corp LP, College Station, TX, USA) with its SVY (survey data) commands utilizing these three stages were used for all analyses, thus ensuring that inferences can be made to the target US population with adjusted standard errors and confidence intervals. Bivariate analyses were used to examine differences at the time of hysterectomy between demographic variables, other diagnoses, complications, mean length of stay and costs with respect to women with and without VWD.

Multivariate generalized linear models with a binomial distribution (logistic regression) were used to examine the risk-adjusted differences between women with and without VWD. Adjusted variables included the potential confounders of age, race, year of procedure, geographical region and median household income for the patient's ZIP code. For all comparisons and regressions, statistical significance was assigned at the $P < 0.05$ level.

Results

During the period from 1988 to 2004, there were 1 358 133 hysterectomies performed in the United States for benign gynaecological conditions – 545, or 1 out of every 2500 hysterectomies, were to women with VWD and 1 357 588 were to women without VWD. The women with VWD were more likely to be younger (mean age 40.58 vs. 46.75 years), more likely to be white (66.79% vs. 51.01%) and more likely to come from a ZIP code (community) with a higher per capita annual income than women without VWD (Table 1).

Women with VWD were more likely to have a diagnosis of abnormal menstrual bleeding (51.56% vs. 31.14%) and less likely to have a diagnosis of uterine leiomyoma or fibroids (40.00% vs. 46.39%) compared with women without VWD, but it is still remarkable that 40% of the women with VWD also had a diagnosis of fibroids (Table 2).

In the bivariate analyses, women with VWD were more likely to experience intraoperative and postoperative bleeding (2.75% vs. 0.86%) and more likely to undergo transfusion

(7.34% vs. 2.13%) than women without VWD, but they were no more likely to experience other wound complications or infection (Table 3). The rate of thromboembolic complications (deep vein thrombosis, pulmonary embolism, myocardial infarction and stroke) was low (<0.2%) among the women without VWD. There were no thromboembolic events among the women with VWD. Women with VWD had a significantly higher cost of hospitalization than women without VWD (Table 4). One woman out of the 545 with VWD (0.18%) died (cause unknown) compared to 0.13% of the women without VWD.

Multivariate regression analysis was used to assess VWD as an independent explanatory variable for complications in women undergoing hysterectomy for the reason of heavy menstrual bleeding. After controlling for the confounders of age, race, year of procedure, geographical region and median household income for the patient's ZIP code, women with VWD were still significantly more likely to experience intraoperative or postoperative bleeding (odds ratio = 2.63), and require transfusion (odds ratio = 5.96) and than their unaffected counterparts (Table 5).

Discussion

The reported prevalence of VWD depends on the population studied and the definition of disease used. We found the frequency of a diagnosis of VWD among women undergoing hysterectomy in the United States to be 0.04% or one in 2500. This figure is lower than the expected prevalence based on identification of persons with bleeding symptoms, low von Willebrand factor and a positive family history, which has been estimated to be between 0.6% and 1.3% [14–16], but is four to 20 times higher than the expected prevalence based on the number of symptomatic patients seen at haemostasis centres, which is 0.002–0.01% [17]. One explanation for the higher prevalence found in this study compared to the estimate based on patients seen at haemostasis centres is that many patients with VWD are not seen in haemostasis centres. One explanation for the lower prevalence compared with the prevalence of persons with a combination of bleeding symptoms, low von Willebrand factor and a positive family history is that the disease is grossly under-diagnosed.

We found the prevalence of VWD to be higher among white women (one in 2000 women) compared to African American women (one in 7000 women). A lower prevalence of VWD in African American women has previously been reported [18–21]. The most likely explanation for this finding is that African American women have higher levels of von Willebrand factor antigen [22] and are less likely to have the disease. The prevalence of VWD among Hispanic women was one in 4000 women, intermediate between white and African American women.

As previously reported, we found that women with VWD undergo hysterectomy at a younger age. We found that the indication for hysterectomy is more likely to be heavy menstrual bleeding or menorrhagia rather than any other diagnosis. We found that women with VWD are less likely to have a diagnosis of fibroids than women without VWD, but 40% of women with VWD still have a diagnosis of fibroids. Recommendations to test women with menorrhagia for an underlying bleeding disorder are often limited to cases of 'unexplained' heavy menstrual bleeding. The data in this study suggest that fibroids and an underlying bleeding disorder frequently coexist and that the presence of fibroids or other uterine pathology does not exclude the presence of VWD or other underlying bleeding disorder.

We found, as previously reported, that women with VWD who undergo hysterectomy are more likely to experience intraoperative and postoperative bleeding and are more likely to require transfusion than women without VWD, but the rates of bleeding were lower than

previously published in three other studies [3,10,11] that reported on bleeding complications among women with VWD undergoing hysterectomy. As the women in the present study had diagnosed cases of VWD, perhaps providers, in most cases, were able to anticipate the possibility of haemorrhage and provide prophylaxis resulting in a lower rate of bleeding complications. Another possible explanation for the lower rates of bleeding complications in this study is that in previous studies, subjects were probably patients at a haemostasis or haemophilia centre, where patients with more severe disease are likely to be seen. The rates, however, were lower for both cases and controls. In a study published by Silwer from 1973 [10], 22% of women with VWD undergoing hysterectomy and 8% of women without VWD experienced intraoperative and postoperative bleeding, remarkably higher than the 2.75% of women with VWD and 0.86% of women without VWD found in our study. In the other studies, the rates of bleeding complications were based on retrospective chart review or patient recall, which may explain the higher rates compared with the rates in the present study.

Thromboembolic events are rare among women undergoing hysterectomy for benign gynaecological conditions. The risk may be even lower among women with VWD, but a difference could not be demonstrated in this study.

There are several limitations to this study. Data were limited to the data in the Nationwide Inpatient Sample (NIS) which are derived from discharge record abstractions, allowing for the possibility of errors in coding. Nonetheless, the NIS is the most reliable source of US data on hospital admissions and discharges [12,13]. As the women who had a diagnosis of VWD had sufficiently symptomatic disease for the condition to be mentioned in their medical records, the results of this study are likely to be biased toward more symptomatic cases of VWD. As data were derived from discharge record abstractions, detailed and precise information was not available to validate the diagnosis (or type or severity) of VWD, specific treatments or other complications. Compared with other diseases, VWD is difficult to diagnose. Also, the nature of the database does not allow for the verification of missing data, nor does the nature of the database allow for the identification of individual women, preventing linkage to other databases, which might provide additional information about diagnosis and treatment, such as laboratory values or medications. Additionally, the discharge record abstractions do not allow for attribution of the timing of events. It is possible that transfusions were administered for prevention rather than for treatment of bleeding. The higher costs of hospitalization may have been due to the costs of prophylaxis rather than treatment of bleeding complications. A next step would be a prospective study of women with VWD who are undergoing hysterectomy to determine bleeding complications according to their type of VWD, level of von Willebrand factor and type of prophylaxis.

Despite its limitations, the NIS, with its large numbers of cases, allowed for the estimation of the incidence of bleeding and other complications in this study. Data were collected prospectively and therefore not subject to selection bias or patient recall, a limitation of other studies. We were able to ascertain that women with VWD who undergo hysterectomy are at a significantly increased risk of intraoperative and postoperative bleeding complications, transfusion and, possibly, death.

In general, women with VWD and heavy menstrual bleeding who have not completed childbearing should be managed with hormonal or hemostatic therapy, whenever possible. Women with VWD who have completed childbearing should be offered the less invasive option of endometrial ablation. Nonetheless, despite the increased risk of complications, the rates are relatively low and only one death occurred in 545 women. Therefore, for women with VWD who have completed childbearing and ultimately require hysterectomy, the risks may be considered acceptable.

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References

1. 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. Thromb Haemost. 1995; 74:784–90. [PubMed: 8585022]
2. Greer IA, Lowe GD, Walker JJ, Forbes CD. Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. Br J Obstet Gynaecol. 1991; 98:909–18. [PubMed: 1911610]
3. Ragni MV, Bontempo FA, Hassett AC. von Willebrand disease and bleeding in women. Haemophilia. 1999; 5:313–7. [PubMed: 10583512]
4. Lak M, Peyvandi F, Mannucci PM. Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand disease. Br J Haematol. 2000; 111:1236–9. [PubMed: 11167767]
5. Kouides PA, Phatak PD, Burkart P, et al. Gynaecological and obstetrical morbidity in women with type I von Willebrand disease: results of a patient survey. Haemophilia. 2000; 6:643–8. [PubMed: 11122390]
6. Kirtava A, Drews C, Lally C, Dilley A, Evatt B. Medical, reproductive and psychosocial experiences of women diagnosed with von Willebrand's disease receiving care in haemophilia treatment centres: a case–control study. Haemophilia. 2003; 9:292–7. [PubMed: 12694520]
7. Perry JJ, Alving BM. von Willebrand's disease. Am Fam Physician. 1990; 41:219–24. [PubMed: 2403725]
8. Woods AI, Meschengieser SS, Blanco AN, et al. Clinical features and laboratory patterns in a cohort of consecutive Argentinian patients with von Willebrand's disease. Haematologica. 2001; 86:420–7. [PubMed: 11325650]
9. Federici A. Diagnosis of von Willebrand disease. Haemophilia. 1998; 4:654–60. [PubMed: 9873810]
10. Silwer J. von Willebrand's disease in Sweden. Acta Paediatr Scand Suppl. 1973; 238:1–159. [PubMed: 4550005]
11. 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; 5:40–8. [PubMed: 10215946]
12. Agency for Healthcare Research and Quality. Overview of the Nationwide Inpatient Sample (NIS) 2000. Rockville, MD: Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality; 2002. p. 1-24.
13. Agency for Healthcare Research and Quality. Introduction to the Nationwide Inpatient Sample (NIS) 2002. Rockville, MD: Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality; 2004. p. 1-31.
14. Biron C, Mahieu B, Rochette A, et al. Preoperative screening for von Willebrand disease type 1: low yield and limited ability to predict bleeding. J Lab Clin Med. 1999; 134:605–9. [PubMed: 10595788]
15. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood. 1987; 69:454–9. [PubMed: 3492222]
16. Werner EJ, Broxson EH, Tucker EL, Giroux DS, Shults J, Abshire TC. Prevalence of von Willebrand disease in children: a multiethnic study. J Pediatr. 1993; 123:893–8. [PubMed: 8229521]
17. Sadler JE, Mannucci PM, Berntorp E, et al. Impact, diagnosis and treatment of von Willebrand disease. Thromb Haemost. 2000; 84:160–74. [PubMed: 10959685]

18. James AH, Jamison MG. Bleeding events and other complications during pregnancy and childbirth in women with von Willebrand disease. J Thromb Haemost. 2007; 5:1165–9. [PubMed: 17403089]

19. Dilley A, Drews C, Miller C, et al. von Willebrand disease and other inherited bleeding disorders in women with diagnosed menorrhagia. Obstet Gynecol. 2001; 97:630–6. [PubMed: 11275041]

20. James AH, Lukes AS, Brancazio LR, Thames E, Ortel TL. Use of a new platelet function analyzer to detect von Willebrand disease in women with menorrhagia. Am J Obstet Gynecol. 2004; 191:449–55. [PubMed: 15343220]

21. Philipp CS, Dilley A, Miller CH, et al. Platelet functional defects in women with unexplained menorrhagia. J Thromb Haemost. 2003; 1:477–84. [PubMed: 12871453]

22. Miller CH, Dilley A, Richardson L, Hooper WC, Evatt BL. Population differences in von Willebrand factor levels affect the diagnosis of von Willebrand disease in African-American women. Am J Hematol. 2001; 67:125–9. [PubMed: 11343385]

Table 1

Descriptive statistics of women undergoing hysterectomy.

Variable	Category	With VWD (*n* = 545)	Without VWD (*n* = 1 357 588)	*P*-value*
Age, mean (IQR)		40.58	46.75	<0.001
		34–46	39–52	
Race, *n* (%)	White	364	692 576	<0.001
		66.79	51.05	
	Black	17	121 045	
		3.12	8.92	
	Hispanic	16	68 663	
		2.94	5.06	
	Other	10	38 817	
		1.83	2.86	
	Race missing	138	436 496	
		25.32	32.15	
Annual income (%)†				
<$36 000		51.01	64.03	<0.001
$36 000–$45 000		25.32	19.60	
> $45 000		18.17	9.54	

VWD, von Willebrand disease; IQR, interquartile range.

*Two-sample *T*-test for age, otherwise chi square test.

†Based on median income in ZIP code of residence.

Table 2

Reasons for hysterectomy among women with von Willebrand disease (VWD) compared to women without VWD.

	ICD-9 codes	Number in women with VWD (% of women with VWD)	Number in women without VWD (% of women without VWD)	*P*-value*
Abnormal menstrual bleeding	626.2, 626.4, 626.6, 626.8, 627.0, 627.1	281 (51.56)	422 767 (31.14)	<0.001
Uterine leiomyoma	218, 218.1, 218.9	218 (40.00)	629 852 (46.39)	0.003
Uterine polyp	621.0	22 (4.04)	60 935 (4.49)	0.611
Endometrial hyperplasia	621.3	14 (2.57)	48 442 (3.57)	0.209
Endometriosis	617	2 (0.37)	12 768 (0.94)	0.259

* Chi square and Fisher's exact test.

Table 3

Complications of hysterectomy among women with von Willebrand disease (VWD) compared to women without VWD.

Outcome	ICD-9 codes	Number in women with VWD (% of women with VWD)	Number in women without VWD (% of women without VWD)	*P*-value*
Intraoperative and postoperative bleeding	998.11, 998.12	15 (2.75)	11 678 (0.86)	<0.001
Transfusion	99.00, 99.01, 99.02, 99.03, 99.04, 99.05, 99.06, 99.07, 99.08, 99.09	40 (7.34)	28 957 (2.13)	<0.001
Infection	038.0, 038.1, 038.3, 038.4, 038.8, 038.9, 686.9, 790.7, 966.6, 998.5, 998.51, 998.59,	4 (0.73%)	5203 (0.38)	0.159
Other wound complications	998.3, 998.83	2 (0.37)	1997 (0.15)	0.192
Thromboembolic complications				
Deep vein thrombosis	453.4, 453.41, 453.42, 453.9	0	150 (0.01)	1.000
Pulmonary embolism	415.1, 415.11, 415.19	0	1343 (0.10)	1.000
Myocardial infarction	410, 410.1, 410.2, 410.3, 410.4, 410.5, 410.6, 410.7, 410.9	0	117 (0.01)	1.000
Stroke	433, 434, 434,91, 435, 435,9, 436, 437, 997.02	0	413 (0.03)	1.000
Death		1 (0.18)	1798 (0.13)	0.515

*Chi square or Fisher's exact test.

Table 4

Mean length of stay and inflation adjusted cost of hysterectomy for women with and without von Willebrand disease (VWD).

	With VWD	Without VWD	*P*-value*
Mean length of stay in days	3.68	3.49	0.0877
Inflation adjusted cost	$19 583.84	$13 224.87	<0.001

*Two-sample Wilcoxon rank-sum (Mann–Whitney) test.

Table 5

Risk-adjusted multivariate analysis* of complications in women who underwent hysterectomy for the reason of abnormal menstrual bleeding.

Outcomes	Odds ratio and 95% confidence interval	*P*-value*
Intraoperative and postoperative bleeding	2.63 (1.24, 5.59)	0.012
Transfusion	5.96 (3.93, 9.03)	<0.001
Infection	1.64 (0.23, 11.69)	0.623

*Referent group is women without von Willebrand disease (VWD). Adjusted variables include age age, race, year of procedure, geographical region and median household income for the patient's ZIP code.